



**SAJOUS'S**  
**ANALYTIC CYCLOPEDIA**  
OF  
**PRACTICAL MEDICINE**

BY  
**CHARLES E. de M. SAJOUS, M.D., LL.D., Sc.D.**

AND  
**LOUIS T. de M. SAJOUS, B.S., M.D.**

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## CONTRIBUTORS TO VOLUME II

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ANDERS, JAMES M., M.D., PH.D., LL.D.  
BEHAN, R. J., M.D.  
BELTRAN, BASIL R., A.B., M.D.  
BONDURANT, EUGENE D., M.D.  
BROWN, CLAUDE P., M.D.  
COLEY, WILLIAM B., A.M., M.D.  
COLLINS, JOSEPH, M.D.  
DERCUM, FRANCIS X., A.M., M.D., PH.D.  
GORDON, ALFRED, M.D.  
GORDON, WILLIAM S., M.D.  
HITCHENS, A. PARKER, M.D.  
JACKSON, EDWARD, A.M., M.D.  
MATAS, RUDOLPH, M.D., LL.D.  
NICHOLSON, PERCIVAL, M.D.  
PETER, LUTHER C., A.M., M.D., Sc.D.  
PRITCHARD, W. BROADDUS, M.D.  
SAJOUS, CHARLES E. DE M., M.D., LL.D., Sc.D.  
SAJOUS, LOUIS T. DE M., B.S., M.D.  
SOLIS-COHEN, SOLOMON, A.M., M.D.  
TORREY, ROBERT G., M.D.  
ZABRISKIE, E. G., M.D.



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Barium .....	426	Etiology .....	481	Preparations and Dose .....	426	Complications .....	481	Physiological Action .....	426	Treatment .....	482	Barium Poisoning .....	426	Blood-pressure .....	484	Treatment .....	427	Systolic and Diastolic Pressure .....	484	Therapeutics .....	427	Pulse-pressure .....	484	Basal Metabolism .....	428	Importance and Applications of the Blood-pressure .....	484	Apparatus and Technic .....	428	Historical .....	485	Clinical Findings and Applications .....	430	Methods of Measuring Blood-pressure .....	486	Belladonna .....	433	Choice of an Instrument .....	490	Preparations and Doses .....	433	The Basis of Blood-pressure .....	493	Incompatibles .....	434	Physiological Variations in Blood-pressure .....	494	Physiological Action .....	434	Blood-pressure in Disease .....	498	Atropine Poisoning .....	440	Hypertension .....	498	Treatment .....	441	Diseases with Hypertension .....	500	Therapeutics .....	443	Therapeutics of Hypertension .....	505	Benzoin; Benzoic Acid and the Benzoates .....	451	Hypotension .....	508	Preparations and Doses .....	451	Treatment of Hypotension .....	512	Physiological Action .....	452	Blood Transfusion. See Venesection.		Poisoning by Benzoin Preparations .....	453	Blood-vessels, Diseases of. See various diseases of this class:		Therapeutics .....	453	Aneurism, Arteriosclerosis, etc., and Vascular System, Diseases of.		Benzol .....	454	Injuries of. See Vascular System: Injuries and Wounds of Vessels.		Physiological Action .....	454	Blood-vessels, Tumors of .....	514	Poisoning .....	455	Definition .....	514	Therapeutics .....	455	Varieties .....	514	Benzyl Benzoate .....	455	Angiomata, or Hemangiomata .....	514	Administration .....	455	General Histology .....	520	Physiological Action .....	456	Etiology and Pathogenesis .....	522	Therapeutics .....	456	Distribution .....	526	Beriberi .....	456	Topographic Distribution .....	528	Definition .....	456	Head .....	528	Symptoms .....	457	Neck .....	531	Diagnosis .....	458	Breast .....	531	Etiology .....	459	Upper Extremities .....	532	Pathology .....	461	Lower Extremities .....	533	Prognosis .....	462	Splanchnic, or Visceral, Angiomata .....	534	Treatment .....	462	General Diagnosis .....	536	Betanaphthol .....	465	General Prognosis .....	537	Mode of Administration .....	465	Treatment .....	538	Physiological Action .....	465	Compression Methods .....	538	Therapeutic Uses .....	465	Superficial Cauterization .....	539	Bismuth .....	465	Freezing .....	541	Preparations and Doses .....	465	Penetrating, or Interstitial, Cauterization .....	543	Physiological Action .....	467	Agents which act by Coagulation .....	543	Bismuth Poisoning .....	468	Physical Agents which Excite Trophic and Nutritive Changes .....	546	Treatment of Bismuth Poisoning .....	471	X-rays .....	547	Therapeutics .....	472	Radium .....	547	Blastomycosis .....	475	Surgical Methods .....	550	Definition .....	475	Bones, Diseases of .....	557	Symptoms .....	476	Rickets, or Rachitis .....	557	Etiology and Pathology .....	476	Definition .....	557	Diagnosis .....	477			Treatment .....	479			Bleeder's Disease. See Hemophilia.				Bleeding. See Venesection.				Blepharitis .....	480			Definition .....	480			Non-ulcerative Blepharitis .....	480																		
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Physiological Action .....	426	Treatment .....	482	Barium Poisoning .....	426	Blood-pressure .....	484	Treatment .....	427	Systolic and Diastolic Pressure .....	484	Therapeutics .....	427	Pulse-pressure .....	484	Basal Metabolism .....	428	Importance and Applications of the Blood-pressure .....	484	Apparatus and Technic .....	428	Historical .....	485	Clinical Findings and Applications .....	430	Methods of Measuring Blood-pressure .....	486	Belladonna .....	433	Choice of an Instrument .....	490	Preparations and Doses .....	433	The Basis of Blood-pressure .....	493	Incompatibles .....	434	Physiological Variations in Blood-pressure .....	494	Physiological Action .....	434	Blood-pressure in Disease .....	498	Atropine Poisoning .....	440	Hypertension .....	498	Treatment .....	441	Diseases with Hypertension .....	500	Therapeutics .....	443	Therapeutics of Hypertension .....	505	Benzoin; Benzoic Acid and the Benzoates .....	451	Hypotension .....	508	Preparations and Doses .....	451	Treatment of Hypotension .....	512	Physiological Action .....	452	Blood Transfusion. See Venesection.		Poisoning by Benzoin Preparations .....	453	Blood-vessels, Diseases of. See various diseases of this class:		Therapeutics .....	453	Aneurism, Arteriosclerosis, etc., and Vascular System, Diseases of.		Benzol .....	454	Injuries of. See Vascular System: Injuries and Wounds of Vessels.		Physiological Action .....	454	Blood-vessels, Tumors of .....	514	Poisoning .....	455	Definition .....	514	Therapeutics .....	455	Varieties .....	514	Benzyl Benzoate .....	455	Angiomata, or Hemangiomata .....	514	Administration .....	455	General Histology .....	520	Physiological Action .....	456	Etiology and Pathogenesis .....	522	Therapeutics .....	456	Distribution .....	526	Beriberi .....	456	Topographic Distribution .....	528	Definition .....	456	Head .....	528	Symptoms .....	457	Neck .....	531	Diagnosis .....	458	Breast .....	531	Etiology .....	459	Upper Extremities .....	532	Pathology .....	461	Lower Extremities .....	533	Prognosis .....	462	Splanchnic, or Visceral, Angiomata .....	534	Treatment .....	462	General Diagnosis .....	536	Betanaphthol .....	465	General Prognosis .....	537	Mode of Administration .....	465	Treatment .....	538	Physiological Action .....	465	Compression Methods .....	538	Therapeutic Uses .....	465	Superficial Cauterization .....	539	Bismuth .....	465	Freezing .....	541	Preparations and Doses .....	465	Penetrating, or Interstitial, Cauterization .....	543	Physiological Action .....	467	Agents which act by Coagulation .....	543	Bismuth Poisoning .....	468	Physical Agents which Excite Trophic and Nutritive Changes .....	546	Treatment of Bismuth Poisoning .....	471	X-rays .....	547	Therapeutics .....	472	Radium .....	547	Blastomycosis .....	475	Surgical Methods .....	550	Definition .....	475	Bones, Diseases of .....	557	Symptoms .....	476	Rickets, or Rachitis .....	557	Etiology and Pathology .....	476	Definition .....	557	Diagnosis .....	477			Treatment .....	479			Bleeder's Disease. See Hemophilia.				Bleeding. See Venesection.				Blepharitis .....	480			Definition .....	480			Non-ulcerative Blepharitis .....	480																										
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# SAJOUS'S

## ANALYTIC CYCLOPEDIA

### of PRACTICAL MEDICINE

#### A

**ANOREXIA NERVOSA.**—**DEFINITION.**—The word anorexia, which is derived from a Greek word *ἀρεξίς* and *a* privative means literally "without longing." It has been used to signify deficiency or loss of appetite for food.

**GENERAL CONSIDERATIONS.**—The symptom is one which, as is well known, is met with in a variety of conditions, such as disease of the digestive tract, organic and functional, in febrile states, in states of great exhaustion, in the cachexia of malignant disease, in various insanities, in psychasthenia, and in hysteria. The term anorexia nervosa was first employed by Sir William Gull in a paper before the Clinical Society in 1874. According to Gull, the affection manifested itself at times by a disgust for animal food especially and at times in its more pronounced forms in a disgust for all foods. The patient is irritable, obstinate, and restless, sleep is much disturbed, and the affection is at times so pronounced as to threaten life unless medical measures intervene. Gull considered the affection as a nervous one in which especially the vagus is involved. Gull's observations were

soon confirmed and extended by Lasègue, Charcot, Huchard, Sollier, and others, and the term anorexia nervosa has come to signify in reality the loss of appetite met with in hysteria; in other words, it is synonymous with anorexia hysterica.

Anorexia nervosa is, as a rule, readily differentiated from the loss of appetite met with in organic disease of the stomach, catarrh, atony, and allied disorders, and from the anorexia met with in cachectic, diathetic, and exhausted states. Its differentiation from the anorexia met with in other nervous affections, while in reality equally clear, demands a moment's consideration. The one nervous affection in which loss of appetite is a common and pronounced symptom and often rises to the degree of absolute refusal of food is melancholia. In melancholia, anorexia is so common a symptom as to be almost as characteristic as the depressive mental state itself. So common is it that it has come to be known by a special term, *sitophobia*, and the symptom ranks in importance almost with the delusion of the unpardonable sin. It is to be distinguished from anorexia nervosa by the differentiation between

hysteria and melancholia. It is invariably associated with the state of painful emotional depression, begins when this begins, becomes more pronounced as this becomes more pronounced, and lessens as this lessens and fades away. Even in melancholia without delusions and without hallucinations, melancholia *sine delirio*, this one feature will serve to differentiate the anorexia from anorexia nervosa. It is only in subacute and lucid melancholia, hypomelancholia, that a difficulty might arise. Here again, however, the anorexia, in keeping with the lessened degree of mental depression, is itself less pronounced; though it must not be forgotten that even patients with hypomelancholia may attempt suicide by starvation. It must be remembered that the mere absence of hysterical stigmata will not serve to differentiate such a case, as anorexia nervosa may be the only outward or tangible manifestation of hysteria. The hysterical mental attitude is however always present;—the abnormal suggestibility and emotional mobility.

As regards neurasthenia, the question of anorexia practically never arises, for in the neurasthenic, despite the digestive disturbances, the appetite is uniformly or almost uniformly exaggerated; never lost. The same is true of psychasthenia; here the appetite is also usually exaggerated, and indeed in some instances amounts to a bulimia. However, in a limited number of cases, because of the atonic indigestion usually present (associated as this is with slowness of digestion, distention, belching, and perhaps regurgitation) the patient may develop a refusal of food, *i.e.*, an obsession with regard to food, or he

may develop a special fear in regard to eating. Indeed, Buvat has pointed out that anorexia occurring in a psychasthenic is the expression of a phobia. As already stated, it is quite rare.

**SYMPTOMS.**—A consideration of anorexia nervosa necessitates a consideration, however brief, of the nature of hysteria, of which anorexia nervosa is but a symptom. Hysteria may be briefly defined as a nervous affection the various symptoms of which bear the impress of a psychic origin. How thoroughly this conception of hysteria has taken hold of the modern medical mind is evidenced by the views advanced by Babinski.

Babinski holds, as is well known, that hysteria has its origin entirely in suggestion, and that its symptoms are curable by persuasion, and he has introduced as a name for the affection the term *pithiatism*, which literally means curable by persuasion. However, whether we accept the radical interpretation of Babinski or not, the fact of the psychic origin of the symptoms must ever be borne in mind. These symptoms embrace the range of those possible under the circumstances, and, therefore, include not only mental, motor, and sensory symptoms, but also visceral symptoms (see article on Hysteria). That in hysteria, therefore, we should meet with involvement of the digestive tract is not surprising. It is perfectly conceivable that, just as an arm may be hysterically paralyzed, *i.e.*, elided from the field of conscious activity as regards its motion and sensation, so may the organic sensation of hunger, the desire for food, be elided, cut out of the consciousness of the patient. Again, it is conceivable that, just as

hysterical pain may occur in the head, the trunk, or a limb, so may it occur in a viscus and that viscus the stomach. Further, it is extremely probable that the mucous membrane of the stomach is every now and then the seat of areas of painful hyperesthesia identical in nature with the painful stigmata found upon the skin, such as the inframammary and inguinal tenderness. We know definitely that such areas are found on all the mucous membranes accessible to our observation, namely, the conjunctiva, the mucous membrane of the mouth, the nose, the pharynx, the vagina, the rectum. That they equally make their appearance in less accessible structures, such as the stomach and bladder, there is in my mind no doubt.

Anorexia nervosa is usually present in association with other and unmistakable signs of hysteria. However, if the anorexia nervosa be very pronounced, the other signs become less prominent and may even fade away. Indeed, as already stated, anorexia nervosa is now and then the only objective or tangible symptom present except, of course, the one cardinal symptom, the attitude of mind.

As a rule, anorexia nervosa develops gradually and its early signs may be insignificant and attract but little attention. Thus, it may make its appearance in a case of hysteria in which other well-marked hysterical manifestations are already developed. In such instance it may merely complicate the existing condition, and quite commonly anorexia making its appearance under such circumstances is not very pronounced and may even prove transitory. However, when it makes its appearance as an inde-

pendent or as the first well-marked symptom of hysteria, it may prove very persistent and obstinate. Equally true is this of cases in which anorexia makes its appearance in the midst of other well-established symptoms, but gradually substitutes these symptoms so that after a while it alone remains, —either alone or as the most prominent symptom.

The first objective symptom of anorexia nervosa is a diminution of the appetite. This diminution becomes gradually more and more pronounced until finally a complete refusal or disgust for food is developed. If in response to the urging of physician and friends food is taken, it is taken with apparent effort, often with exaggerated attempts at swallowing, usually with spitting up of the food, actual regurgitation, and finally vomiting. This vomiting, as is well known, may be very obstinate and may follow every attempt to administer food. Curiously enough, though this is the exception, a patient under these circumstances may declare herself to be hungry,—hungry and yet unable to eat. In the average case, however, all instinctive feeling for food seems to disappear; hunger and thirst are equally absent. Strangely, too, food, even when retained, may not give rise to the normal sensation of satiety.

At times the disgust for food is so pronounced that the patient cannot bear even to think of taking food; the mere suggestion of food is followed by manifestations of disgust and nausea. It would seem also that during the height of an attack of anorexia nervosa the patient is often unable to recognize the food properly. There is quite commonly complaint

## ANOREXIA NERVOSA (DERCUM).

that the food tastes bad or that it is disgusting: the eggs are not fresh, the milk has turned, the meat is tainted, there is something in the broth, the water tastes of gas, etc.

While cases of anorexia bear a general resemblance to each other, marked differences may obtain, both as to the mode of origin and as to the severity or the details of the symptoms. Thus in one group of cases, as has been already indicated, there is primarily a disturbance of the organic sensations of hunger and thirst or an actual elision of these sensations. There is in these cases not the fundamental disgust for food so commonly met with in the other forms. Not infrequently too, such a patient, having been induced to eat, feels the appetite returning. In other words, the normal desire for food returns when the mere mechanism of the taking of food and digestion is set in motion. Such cases are comparable to the disappearance of an hysterical retention of urine by the suggestion furnished by running water, or the disappearance of an hysterical palsy by the institution of passive movements. As would seem probable on *a priori* grounds such cases yield, as a rule, quite readily to treatment and are rarely persistent unless complicated by untoward and inadvertent suggestions.

More commonly, however, cases of anorexia nervosa are not so simple. In by far the larger number of cases the origin is somewhat as follows: The patient complains usually for a time that food gives rise to pressure, to pain, to distention, to gas usually in great quantities, and upon this basis develops a loss of appetite, fear and disgust of food. Pain may be referred to various regions of the

stomach, and this pain may be associated with tenderness, an hysterical hyperalgesia. This tenderness is most frequently marked in the pit of the stomach. It apparently is in the stomach, probably in its mucous membrane, and as already indicated is analogous to the painful areas found upon the cutaneous surfaces. Physicians sometimes describe cases presenting these symptoms as gastralgia, failing to recognize their hysterical character. Further, the epigastric tenderness, it should be borne in mind, must not be confounded with the pain met with in gastric ulcer. However, gastric ulcer may be simulated, especially if there be present spitting of blood, a symptom that some hysterical patients appear to be very expert in producing. It is hardly necessary to point out here the necessity, in given cases, for an analysis of the gastric contents, microscopical and chemical, in making the differential diagnosis.

The most difficult cases of anorexia nervosa are those in which pain makes its appearance immediately after the introduction of food, or in which hysterical distention immediately ensues. The latter symptom is sometimes pronounced to an incredible degree. At times, a small quantity of milk or even a swallow of water is followed by a violent and excessive distention of the stomach and, in a case recently under my observation, by an enormous ballooning of the entire abdomen, rapid pulse, and difficult breathing. In other cases, the patient does not complain of pain and does not manifest distention, but the taking of food results in restlessness, fear, palpitation, sweating, faintness, or in the onset of hysterical crises

which have gagging, retching, regurgitation, or vomiting as their central features.

As a rule, by the time that these patients reach the physician's care, they have narrowed their diet to an extreme degree. Frequently it has become limited to a small amount of liquid food, or, as in another patient recently studied by me, to a few teaspoonfuls of ice-cream daily. That great loss of weight and even marked emaciation may ensue under such circumstances goes without saying.

There is a third group of cases, in which the anorexia nervosa has still another mode of origin. Here the anorexia is the outgrowth of unhealthy ideas, unphysiological notions on the part of the patient. Very many women entertain the idea that they must not become stout, that they must preserve their shape, that it is vulgar to be fat, and that it is gross to eat much. Given these ideas and the hysterical neurosis, extreme and difficult anorexia nervosa may result. Many a patient already absurdly thin views with the utmost alarm the slightest possible addition to her weight and obstinately resists the administration of food, if only in physiological quantities. In other cases, a smaller number, the patient has acquired the absurd notion that the free taking of food is not healthy, and that body and mind are both best off when the food is very limited in amount. Usually vanity of figure is again the real explanation. The patients of this group are usually extremely difficult. They are invariably far below weight. By the time they come under medical care, their diet has become very restricted. They have usually adopted some special

form of diet, or have developed obsessive ideas in regard to the most ordinary and most wholesome foods. Milk is almost always under ban, and this is usually true of eggs. Sometimes meats are included or it is vegetables which are tabooed; sometimes it is everything or almost everything.

The course of anorexia nervosa when once established, no matter what its mode of evolution, is largely as follows: The patient becomes more and more confirmed in her attitude as regards food. Emaciation becomes more and more pronounced, and her bodily and mental activities become more and more limited. In bad cases they become confirmed bed-ridden invalids who employ their feeble remaining energy to resist the taking of food, and who fight doctor and nurse silently, tenaciously, and at times effectually, for death may actually supervene. Thus, Osler described a fatal case, the patient weighing at the time of death only 49 pounds. The autopsy disclosed nothing. They may get to the stage of refusing to take food altogether voluntarily, and if the attempt be made to feed them with a spoon avert their faces, compress their lips, bury their heads in the pillows. Sometimes hysterical struggling, weeping, collapse may ensue. Other patients will complain that they are too weak to masticate their food, that swallowing tires them, that it makes the blood rush to the head, makes them dizzy, makes them faint. Solid food is first discontinued, and then the liquid foods are gradually restricted until they become grossly insufficient in amount.

The full development of a typical



anorexia nervosa is usually a matter of some time, usually weeks, often months, and occasionally years. The symptom, however, as already stated, may make its appearance spontaneously and rapidly, just as do other hysterical manifestations. Charcot described the case of a girl of 18 who, having witnessed the killing of a child by a railroad train, became sad and depressed, was troubled by distressing dreams. About two months later she lost her desire for food. This loss appeared suddenly and supervened upon an attack of suffocation (*globus hystericus*) while she was in the act of taking food. Upon subsequent attempts to take food, the *globus* promptly reappeared.

It is important to call to mind a few other features. First, while in many cases of anorexia nervosa there is undoubted loss of weight and even emaciation, prolonged refusal of food may coexist with remarkably little loss of weight and strength. In many of these cases, food, of course, is taken and probably in larger amounts than is admitted by the patient. In others the fact that the patient is in a condition of absolute quiet in bed diminishes the actual need for food. In some cases again, fraud can justly be suspected. It is further noteworthy that in cases in which there is but little loss of weight and strength there is usually no vomiting. Secondly, as regards the vomiting, this can hardly be regarded as a genuine automatic ejection of food by the stomach. Nausea, genuine nausea, while it may be claimed, is often absent, and the act by which food is ejected is more like a regurgitation than a genuine vomiting. Sometimes the food is ejected before

it reaches the stomach, a condition which has given rise to the term *esophagismus*. At other times the act of swallowing is evidently imperfectly or spuriously performed. Although the patient seems to make exaggerated efforts, she fails to swallow and declares that the food will not go down. At other times she frankly makes no attempt to swallow the milk or other liquid introduced into the mouth, but allows it to dribble out or frankly ejects it.

Finally, owing to the insufficient ingestion of liquids, the skin may be harsh and dry and the urine greatly diminished in amount and much concentrated.

Nebelthau observed a case of hysterical anorexia in which, while there was no evidence of visceral disease and no sugar in the urine, the breath smelled of acetone, the urine giving a most marked reaction of acetoacetic acid. There was vomiting, and the vomit also contained acetone. With sufficient nutrition the smell of acetone in the breath, the reaction with ferric chloride in the urine, and the increased ammonia excretion disappeared.

The cases of hysteria which present anorexia nervosa, let it be repeated, are almost always young women. While I have met with this symptom in women of middle life, I have never seen it assume a grave form at this age. A similar statement may be made with regard to male patients. While diminution of appetite may be noted among male cases of hysteria, I have personally never seen a case of sufficient gravity to be characterized as an anorexia nervosa. The patient is most frequently a young woman; sometimes a mere child. Two of the worst cases I have ever seen, however, have occurred in women between 30 and 40.

Neisser and Brauning have often observed patients who grew thin because their appetite was appeased with a few mouthfuls of food and they did not care to eat more and consequently were starving although their appetites were good. A research showed that it depended on the pressure within the stomach from the food itself or from the peristaltic contraction of the stomach or from pressure from without as from a tight corset. Beside laying aside the corset, suggestion served to train the young girls to eat normally and enjoy the entire meal with appetite instead of being satisfied with a few mouthfuls, but this once accomplished they rapidly took on weight. In another group of patients early satiation was traced to excessive tonicity of the stomach walls and hasty eating.

**TREATMENT.**—The treatment of anorexia is of course primarily that of the underlying hysteria, and in order that this shall be successfully combated it is of the utmost value, whenever practical, to institute a radical course of rest treatment with complete isolation of the patient included among the measures to be taken. In this connection it must be admitted that Babinski rendered invaluable service to our understanding of hysteria by accentuating the fact that in hysteria suggestion plays an enormous rôle. The indications are to place the patient in whom such profound perversion of function as anorexia nervosa has occurred amid surroundings and under conditions in which it will be possible to bring about a restoration to simple physiological living and at the same time to protect the patient against the evil influences of harmful suggestions such as they are almost always subjected to by their well-meaning, but mistaken relatives and friends. It is quite clear that a **rest treatment** in bed with complete isolation offers the most favorable conditions for the

carrying out of such a plan. For the details of the rest treatment as applied to hysteria in general, the reader is referred to the section which treats with this affection especially. Suffice it to say here that the rest in bed should be absolute and continuous for a time; usually a number of weeks are required. Secondly, simple **bathing** such as will not shock or disturb the patient, bathing with lukewarm or slightly warmer water, carried out between blankets in bed, followed or not, according to circumstances, by a gentle **alcohol rub**. Usually, gentle **massage**, not too vigorous and not too deep, carried out in the latter part of the day, preferably in the evening, before the hour for sleep, proves of great value. In giving the massage, if there be an anorexia nervosa, it is important that the nurse should omit rubbing the epigastrium or the abdomen generally; at least at first because of the painful tenderness so frequently present in the epigastric region. Later on, of course, during convalescence, the massage may include the region of the stomach as well as the abdomen generally. Care should also be exercised by the nurse that in giving the massage she makes no untoward suggestion or comment as to reasons for rubbing certain portions of the trunk and not others. It is unnecessary to add that the nurse should be one who is especially trained in the management of nervous cases.

The views of Babinski are especially to be borne in mind as to the curability of hysterical symptoms by persuasion, a fact, of course, long known, but upon which he has with great justice laid renewed stress. **Persuasion** in all its forms must be

employed, and the suggestion of getting well, both directly and indirectly, must pervade the sick-room.

The *basal metabolism* was found below normal, ranging from 73 to 82 per cent., in 4 women with pronounced anorexia and loss of weight. All were sensitive to cold, and had a slow pulse, with constipation and amenorrhea. Allusion made to Plummer's view that secondary hypothyroidia occurs in cases of inadequate food intake with lowered metabolic rate. E. Moller (Ugeskr. f. Laeger, Feb. 14, 1924).

The treatment of the special symptom of anorexia is one which usually offers many difficulties. No general rule as to the food which should be administered can be given. In many cases much can often be accomplished by making an agreement with the patient as to the kind or kinds of food which shall be first attempted. As a rule, the patient at first rejects every proposition that is made by the physician, but after a little gentle argument and persuasion some basis of agreement can be reached. If possible this should include milk, and, indeed, if it be limited to milk the physician has no great cause for complaint. The patient may insist upon an absurdly small quantity being given at a time. If so, the compromise reached should be adhered to, bearing in mind that much can be gained by frequency of feeding. If milk be rejected, white of egg or albumin water may be attempted, though this must be regarded as merely a temporary expedient. As a rule, the patient becomes accustomed to the food as being given, she feels that no advantage is being taken of her, acquires confidence in both the physician and the nurse, and can be persuaded in the course of a few days to allow the milk

or other liquid food that is being given to be increased. Whether the milk had best be modified in some way, peptonized, skimmed, diluted, made alkaline by the addition of lime water, salted or otherwise flavored, must depend entirely upon the resourcefulness and the tactful judgment of the physician. Suffice it to say that most is gained if whole milk be administered. It may be wise to skim this slightly, so as to diminish the amount of cream which is taken. Sometimes, it is found that if the milk is diluted with some carbonated water, such as Vichy, fountain soda, Apollinaris, and the like, it is well tolerated. Occasionally, cases are met with in which liquids, as well as solids, are equally rejected. In such instance we have to resort to some of the following expedients; for instance, the yolk of an egg which has been very thoroughly boiled may be powdered and mixed with sufficient salt to make it quite salty. Small quantities of this can be placed upon the tongue and the patient encouraged to swallow it. If only a beginning can be made in the way of stimulating the retention of food by the stomach, all is gained, for the patient will soon find that other foods can be retained. At times, a very small quantity of finely minced ham—a mere fragment given by a teaspoon at intervals—will be retained. At other times a small piece of dried beef can be chewed by the patient and the juice swallowed. Later, such a patient can be persuaded to chew a small piece of steak and to swallow the juice. The primal effort and object of all the attempts at feeding should be the restoration of the belief on the part of the patient in her abil-

ity to retain food, and, after all, the various means by which this can be accomplished depend upon the case and must of necessity be very varied. On the whole, medicines had best be avoided, as the patient is apt to reject these as promptly as the food. However, it is not infrequently found that **bromides** are retained when other medicines are not tolerated. If so, much is gained. Twenty grains (1.3 Gm.) of the **bromide of ammonium**, with a little **aromatic spirit of ammonia** dissolved in peppermint water and well diluted, are frequently retained and, as it were, gratefully appreciated. Sometimes this is not the case. Under such circumstances, we now and then find that **morphine** in small quantities is well borne. It should be given in doses of  $\frac{1}{32}$  grain (0.002 Gm.), repeated at intervals of one-half hour to an hour until a gentle sedative impression has been made. Usually this occurs by the time an eighth has been given. Larger doses of morphine may be employed, but their liability to induce nausea of themselves must be borne in mind. As a rule, cases of anorexia bear small doses well. The morphine may be retained if dissolved in a small quantity of water. Sometimes it is best administered in a few drops of **brandy** or in a teaspoonful of iced **champagne**. Gradually the nervousness and anxiety of the patient are allayed, and the retching and vomiting are brought under control. Small quantities of milk can now be given, and, little by little, the patient's confidence in her ability to take food becomes restored.

As already stated, we now and then meet with a deep epigastric tenderness which from the absence of other

signs suggests that the mucous membrane of the stomach is itself the area of a painful hyperesthesia, a true sensory stigma. Small doses of **cocaine** are sometimes beneficial in such cases. It should be administered in a manner similar to the morphine or may indeed be combined with the latter. **Champagne** by itself has not proved in the writer's hands a very successful expedient for the relief of anorexia nervosa. There is no objection, however, to its trial in cases in which all foods fail. **Carbonated water** alone sometimes proves of value.

The patient's confidence in her ability to take food having been somewhat restored, we should be content with giving small quantities, a teaspoonful or a tablespoonful of some liquid food every hour or two being sufficient. A start having been made, the amount can be increased little by little until, after days and it may be weeks, a full feeding is reached. The approach to solid food should, of course, be cautiously made. That it should be soft or semisolid and small in quantity goes without saying. Special effort to please the fancy and the palate may be made, such, for instance, as a very small and very thin sandwich of toast containing between its layers a small quantity of scraped beef, the latter being well salted and flavored, perhaps, in addition with a minute dash of pepper. A sandwich made similarly with a small quantity of the yolk of a hard-boiled egg may also be tried. Minced ham and a small piece of bacon are among the other articles which naturally suggest themselves.

It every now and then occurs that for several days at a time nothing

whatever is retained, and under these circumstances it is proper to resort to **feeding with the nasal or stomach tube**. Especially is this advisable in cases in which the trouble appears to be especially due to difficulty of swallowing, or esophagismus. Quite frequently it is not necessary to resort to this expedient more than once, the mere preparation for the procedure being often sufficient to stimulate the patient to take a small quantity of food naturally. Now and then, tubal feeding in bad cases of anorexia nervosa is unsuccessful because the patient rejects both the tube and milk as fast as they are introduced. In such instances it is perfectly proper to give, twenty minutes before the feeding is attempted, a hypodermic injection consisting of **morphine**,  $\frac{1}{8}$  to  $\frac{1}{4}$  grain (0.008 to 0.016 Gm.), and **scopolamine**,  $\frac{1}{200}$  to  $\frac{1}{100}$  grain (0.0003 to 0.0006 Gm.). As a rule, the sedation and quiet produced by the hypodermic greatly facilitate the giving of tubal feeding, and, a large quantity of food having been given and retained, the victory may have been gained, the patient having become convinced of her ability to retain the food.

Debove insists on the necessity of compelling the patient to eat, by no matter what method. The appetite will return on eating. That a certain amount of **compulsion** is necessary is attested by a case of Drummond's, that of a neurotic young man of 25 years, weighing 70 pounds, who had been lying in bed for five years, and who gained 14 pounds after a month's treatment. Baruch advises **hydrotherapy and lavage of the stomach**.

Hypodermic medication should, of course, be avoided except in exceptional instances. The relief given is very prompt and gratifying, but, as the relief is temporary only, the patient

may soon insist upon a repetition of the dose. Occasionally when bromide and morphine are not tolerated by the stomach, **suppositories of opium** may be administered. These, for obvious reasons, should be used for a short period of time only.

Finally, we may add that it is rarely necessary to resort to **rectal feeding** in anorexia nervosa. If tried, it should be persisted in for a short time only, as the moral effect of the procedure is bad, the patient being confirmed in her opinion that there is something serious the matter with her stomach.

In the average case of anorexia nervosa, the difficulty of administering food is not so profound as would perhaps be implied by the foregoing paragraphs. Most frequently the patient objects strenuously to some special article or articles of diet; strangely enough they are frequently the very articles that the physician most desires to give.

J. P. Crozer Griffith observed a case in a male child in which there was a strong disinclination to try any food which was new to him. He refused to taste ice-water until after his sixth birthday, and then expressed surprise that it was so good. With regard to all new articles of diet, his reasoning was voiced in his remark that "he would not taste it because he had never eaten it before." This expression on the part of the child is clearly the keynote of the whole situation, according to Griffith. Instead of disappearing soon, as is usually the case in convalescent infants, this dislike became intensified, and extended, finally, to all food and methods of giving it, except the two to which the child had already become accustomed, viz., milk sucked from the breast and bread eaten from his own hand. The anorexia was now as marked and clearly as hysterical in nature as that seen in patients of a greater age. Only the **forced feeding**

prevented the excessive emaciation which often occurs in older patients.

[There is in these cases general vasodilation with recession of the blood into the splanchnic area. **Pituitary solution**, injected in 15-minim (1 c.c.) doses daily, with **strychnine** orally in  $\frac{1}{40}$ -grain (0.0016 Gm.) doses to stimulate the adrenals, soon raise the vascular tension and restore the arterial circulation to the tissues.—Ed.]

In a girl of 9 years, a fright had been followed by increasing anorexia, emaciation, melancholia, and great weakness. **Forced feeding** through a stomach tube was resorted to. An opaque meal revealed an atonic stomach and a dilated, diseased appendix. Subsequently **appendectomy** was carried out. Improvement began at once; a year later the child was normal. In case of a distinct aversion to a certain food, protein skin tests are advisable before insisting that it shall be eaten. T. W. Clarke (N. Y. State Jour. of Med., Mar. 14, 1924).

In a neurotic child of 5½ years, whose mother had for months been trying to entice her to take food, the writer overcame the difficulty by telling the child that he was going to have "a great secret" with her; that she and he only would know it; that she was "to eat as much as she possibly could at every meal during the next week," when she was to come and see him again. The child, seemingly delighted at being trusted with a real secret, began to gain rapidly and, receiving no sympathy by refusing food, acquired the habit of eating. Another child, aged 1 year and 5 months, was sent to a nursing home, where she was given food and plainly made to understand that she was expected to eat it immediately and without any fuss. A mixture of **compound tincture of cinchona**, 5 minims (0.3 c.c.); **tincture of nux vomica**, 1 minim (0.06 c.c.), and **potassium bromide**, 2 grains (0.12 Gm.), was given before meals. The parents were informed they would not see the child for a week. She became distinctly hungry, and continued to improve when re-

turned to her home. B. Myers (Pract., Nov., 1924).

Case of anorexia in a girl of 17 years. She had lost 44 pounds in 5 months. Symptoms of disturbed ovarian and thyroid function led to the prescription of **thyroid gland**, without any other treatment. She had partial loss of will power and memory and loss of all affection for her parents and of interest in her personal appearance. All these manifestations rapidly passed off under thyroid and her weight returned to normal. Sédillot (Paris méd., Dec. 19, 1925).

This difficulty may be met in a number of ways. When possible the endeavor should be made to bring about in the patient an **autosuggestion** favoring the dietary it is desirable to prescribe. This, of course, must be accomplished by indirect methods. Thus the article of food, most often it is milk, may be emphatically and ostentatiously forbidden, or the nurse, having been previously instructed, should in the patient's presence mention the matter of milk. The physician in reply should treat this matter as of no consequence or possibly ignore its mention by a shrug of the shoulders. Not infrequently the patient, finding that milk is not being forced upon her or not even mentioned in her presence, asks the physician whether he never in such cases as hers prescribes milk and whether a trial of the milk in her case might not prove beneficial. Especially is this likely to come to pass if the amount of other food has been so limited as to be grossly insufficient. However, the indirect method of suggestion or the suggestion of the opposite not infrequently fails, and here tactful persuasion, the striking of a hard and fast agreement, as already mentioned

above, should be attempted. Almost always it can be secured. The advantage gained is exceedingly great, and if followed up in the proper manner it will prove of enormous usefulness in bringing about a successful issue. Very much, of course, must be left to the tact of the physician and his intimate knowledge of the mental make-up of the patient. The essentially psychic character of the symptoms should never be lost sight of.

F. X. DERCUM,  
Philadelphia.

### ANTHRAX.—DEFINITION.—

A malignant pustule due to infection by the *Bacillus anthracis*, from which, as a focus, the infection may spread over the body or attack the intestinal tract, resulting in a general infection. It is also known as "wool-sorters' disease" in man and "splenic fever" in animals. It is due to specific bacilli which may attack every species of domestic mammal, and may thus become one of the greatest scourges of animal life.

When the lesion occurs in dense, highly vascular superficial tissues of man, it is often termed *anthrax carbuncle* or *malignant pustule*; when it occurs in loose tissues *anthrax edema* is witnessed. *Internal anthrax* refers to lesions of the internal organs.

**SYMPTOMS.**—The most frequent location of the primary lesion is in the face. The first symptom is a sense of itching, followed by a red spot resembling a flea-bite; a small vesicle forms soon afterward, containing a bluish fluid. The surrounding skin is somewhat indurated and swelled. This changes into a black spot, which soon becomes gangrenous. If the

edema continues, fresh crops of vesicles often appear, undergoing the same change, and infecting the adjacent lymphatic glands. The period of incubation is from one to three days, while the development of the local symptoms occupies from three to nine days. A line of demarcation may then form, and the slough separates. No pus is present. General disturbance begins only a day or two after the manifestation of the disease. There may be no fever, but in some cases, especially when the face is involved, a sudden rise of temperature may present itself, denoting a dangerous condition. When located in the eyelids considerable cicatricial deformity may result.

In 5 cases observed by the writer, the infection had followed comparatively slight wounds with crushing of muscle tissue. The path of the projectile was a tract of putrid mortification and edema developed early. It spread to the end of the limb but not up to the trunk. Death occurred from heart failure. Scalone (Polyclinico, Nov., Surg. Sect., 1917).

The vesicles are not observed in every instance. When present they may be few or many and occasionally they are grouped. They usually come out only when the infection is well under way. In spite of the vicious look of the anthrax lesion, the patient rarely complains much of pain. When at rest, he does not seem critically ill. He has a peculiar pallor and appears dull mentally, sometimes a little dazed, but is always conscious. He tires quickly under questioning, and on exertion soon shows marked weakness. There is no fixed constitutional reaction. Some cases die in 48 hours. The diagnosis should be based on what the skin shows rather than on laboratory study. Otherwise, precious hours may be lost. Where laboratory facilities are readily available, however, the organism can as a rule be found quickly in the smear. J. R.

Graham (Monthly Bull., Dept. of Health, City of New York, Nov., 1921).

Case of pulmonary anthrax, in the hospital for 57 days preceding death, in which the lungs showed at necropsy a chronic progressive organizing pneumonia with areas of necrosis. H. H. Bell (Mo. State Med. Assoc. Jour., Dec., 1924).

Headache, nausea, and pain in the muscles appear, with a weak and rapid heart. There is slight icterus. The prostration is great, and the last stages of the disease find the patient almost in the algid stage of Asiatic cholera.

When infection takes place through the alimentary canal, the disease begins with debility, depression of spirits, malaise, and probably a chill. In addition, the symptoms point to the intestines. Hemorrhages occur from the mouth and nose; vomiting is followed by a bloody diarrhea. The diagnosis is, however, extremely difficult, and the microscopic examination of the blood or an inoculation of an animal is alone conclusive.

**Ascoli Reaction.**—This is a precipitin test which can be carried out in a few minutes by simply boiling a little of the infected material in 3 or 5 times the amount of physiologic salt solution and pouring the cooled filtrate on the precipitating serum. The white ring and zone at the point of junction are characteristic for anthrax in cattle and swine plague, while with extracts from pellagra, septicemia or lymphadenitis the reaction is invariably negative. According to Izabolinsky and Patzevitch the reaction occurs even with fluids and tissues which have undergone putrefaction for 40 days, and is most marked when an extract from the spleen is employed.

An essential feature of the Ascoli reaction is the heating of the material for 5 to 10 minutes on a water-bath of boiling water. The test is truly

specific, and should supplement the bacteriologic study. Bornand (Rev. méd. de la Suisse rom., Aug., 1923).

**ETIOLOGY.**—Anthrax was one of the first diseases traced to a specific micro-organism.

Pollender discovered, in 1849, small rod-shaped bodies in the blood of animals suffering from anthrax, but Davaine, in 1863, proved their etiological significance. Pasteur and Koch, observing that the bacilli bore spores, cultivated them successfully outside of the body, and then produced the disease by inoculating animals with the pure cultures.

The anthrax bacilli are large rods, of a rectangular form and square-ended. They measure 5 to 20 microns in length and are 1 to 1.25 microns in breadth. They form long threads, in which the single bacterium can be made out. At times isolated rods occur. In this stage granular bodies appear in the protoplasm of the bacilli. They eventually form glistening oval spores, one of which lies in each segment of the long thread, giving the threads an appearance of a string of beads. The bacilli soon break up, and the spores become free. In this condition the spores become highly resisting and can be preserved a very long time. If again placed under favorable circumstances, each spore will germinate into a mature cell.

Spore formation takes place only at temperatures ranging from 18° to 43° C., 37.5° C. being the most favorable temperature.

The anthrax bacilli can rapidly be stained by aqueous solutions of aniline dyes, and also by Gram's method. The spores are best stained at a high temperature by means of Ehrlich's



aniline-water-fuchsin solution or Ziehl's solution containing phenol.

The virulence of anthrax bacilli can be attenuated in various ways, such as subjecting them to a high or low temperature or making the culture grow for a long time—twenty-four days or so—at a temperature of 42° or 43° C. By treating them in some such manner it is possible to render anthrax bacilli entirely innocuous (Koch, Loeffler). Pasteur rendered sheep and cattle immune against anthrax by inoculating them with a culture which grew at 42° C.

Dogs, pigs, and the majority of birds are immune from anthrax; also rats and frogs under ordinary conditions. But if a frog in whose lymph-sac are placed anthrax bacilli is put in an incubating apparatus, he will quickly die of anthrax. Birch-Hirschfeld and others have proved that anthrax bacilli can be transmitted from mother to fetus *in utero*.

The gastric juice in animals does not affect anthrax spores, which, however, cannot proliferate in the intestinal juices. Upon spraying anthrax germs through the nose, they can be made to reach the lungs without injury to the skin or mucous membrane. If the dose exceeds 100,000 the spores invade the blood, causing septicemia. In smaller doses they remain latent in various organs, but can be made to proliferate and produce "internal anthrax" by the injection of substances inducing necrotic foci, in particular by provocative injections into the spleen 24 hours after the spores have reached the lungs. Alimentary tract lesions in anthrax are hematogenous; when Peyer's patches are affected hemorrhagic necrosis may be produced. Sanarelli (Ann. de l'Inst. Pasteur, Mar., 1925).

The pathogenic germ is disseminated by the excretions of diseased

animals, or by the fluids which escape from carcasses of animals killed by the disease.

Because of the remarkable tenacity with which certain plots of ground retained their infection, Pasteur, in 1880, reached the conclusion that the carcasses of animals dying from anthrax, even though deeply buried, retained their many infectious organisms and supplied them with such an amount of nutriment that they continued to multiply for years, and in this way produced an immense underground supply of virulent anthrax organisms.

The writer found anthrax spores in the earth of a place which had been used 6 years before for burying diseased animals. The *burying ground* was wanted as a playground, and the investigation was undertaken to determine whether it was safe for such use. The writer recovered anthrax bacilli 6 times by animal injections and twice by direct planting. W. v. Gozenback (Zeitsch. f. Hyg. u. Infektionskrankh., lxxix, 336, 1915).

Herds are infected, as a rule, by the ingestion of spores with their food when the latter has been contaminated in the manner described, the spores germinating in the intestines. Cattle and sheep being the animals most frequently infected, the occurrence of disease principally in men who handle the hides or wool of these animals is clearly accounted for. In man, however, infection may occur by the inhalation of infected dust from the raw material they handle as wool sorters. Hence the term, "wool sorters' disease." Infection may occur through abrasions of the skin; in Cyprus, it is known to be transmitted through the bites of an ant-like insect (*sphangi*, Williamson), which obtains the spores from the carcasses of infected animals. It has also been transmitted by bone-dust of such animals (Neave).

Where tanneries are located upon or near to streams there is great danger that anthrax will be brought to them upon hides and then be scattered over the low lands lying downstream from the point where the tanning process is carried on. This state of affairs exists especially near to those tanneries which work upon goat or sheep pelts from foreign countries. Infection in the form of spores adheres to these hides so persistently that ordinary fumigation fails to destroy it, and repeated outbreaks of the disease occur wherever such skins are unpacked and manufactured into leather. In making mention of this danger, Professor Law writes:—

"Since 1892, anthrax has prevailed along the banks of the Delaware River for a distance of forty miles in New Jersey and Delaware, destroying from 70 to 80 per cent. of the farm stock. The great morocco industry on this river draws infected hides from India, China, Russia, Africa, and South America, and the spores are carried and distributed by the hides." H. J. Washburn (U. S. Dept. of Agriculture, Bulletin 439, 1911).

Outbreak of 25 cases observed within 4 months. Of these, 23 occurred in persons handling hides. It was confined to workers in tanneries where dried "China" hides were used. All of the hides had reached America in the same cargo and had come from a district of China in which anthrax was known to be endemic. W. H. Brown and E. Simpson (Jour. Amer. Med. Assoc., Feb. 24, 1917).

Statistics have shown a gradual increase in the yearly total of fatal cases of anthrax in rural districts. Ignorance or dislike of loss may lead to the selling of an infected skin instead of burning or burying it as required.

Insect bites, such as those caused by mosquitoes and stable flies, and commonly used articles such as shaving brushes, sheep skin caps (Rogers)

have been found to transmit the disease. Maitman was able to transmit anthrax with stable flies from infected animals to guinea-pigs, and likewise from sick to healthy guinea-pigs.

To obviate the difficulty in distinguishing rapidly between the true anthrax bacillus and the anthrax-like organisms, the author examines directly with a high power objective the minute structure of the suspected colony. This shows at once the morphology of the organism, whether it is motile or not, whether spores are present, their location and shape if present, and the relation of the organisms to each other. W. H. Hagan (Jour. Bacteriol., July, 1920).

Case in which the shaving brush had been boiled by mistake before examination, but the man's shaving mug was found to contain virulent anthrax bacilli. C. Vincent (Jour. of Inf. Dis., Nov., 1922).

The bacillus can be recovered from the vesicles surrounding the ulcer or, in the internal type, from blood culture, sputum or bloody stool. F. B. Utley (Penna. Med. Jour., Jan., 1923).

Epidemics of anthrax have been prevalent of late among cattle in different sections of the United States, and carelessness in disposing of the bodies inevitably results in a certain number of human cases. With increased precautions taken among workers in hides, infected shaving brushes are the most fertile source of sporadic dissemination. When a recently purchased, cheap shaving brush is found in connection with a case of anthrax, the probability of its being the source is great; confirmatory evidence would accrue from finding anthrax bacilli upon brushes in the same lot as the one used by the patient. The writer estimates the yearly incidence of anthrax in this country at about 153 cases. W. B. Blanton (Va. Med. Mthly., Aug., 1924).

**PROGNOSIS.**—The prognosis of anthrax in man, when infection takes

place externally, depends mainly upon whether appropriate treatment is undertaken early enough. Lengyel and Koranyi, by adopting suitable local treatment, lost only 13 out of 142 cases. Although patients with anthrax resulting from internal infection (intestinal, pulmonary) very rarely recover, the introduction of artificial immunity, active or passive, by the use of vaccines or sera has served to materially decrease the fatality of the disease.

The mortality from anthrax varies within rather wide limits; for example, the malignant anthrax edema of the face and neck is extremely fatal, largely because of infiltration of the soft tissues around the larynx, pharynx, and esophagus. Wool-sorter's disease, an anthrax septicemia with intense pulmonary and cerebral symptoms, and anthrax of the intestinal tract, are likewise deadly. In malignant pustule of the face, however, the mortality is 5 times greater than that of an extremity, in which only about 5 per cent. of cases terminate fatally. D. Symmers (*Interstate Med. Jour.*, xxiv, 1003, 1917).

Study of 31 recorded cases of metastatic meningitis or encephalitis, or both, in anthrax. The writers' case had a pustule above the left eyebrow, and developed cerebral symptoms on the 5th day, dying in 30 hours. Paso and Barni (*Semana méd.*, Jan. 22, 1925).

The presence of bacilli in the blood greatly aggravates the prognosis, although recoveries have been reported.

Anthrax bacilli found in the blood in 7.23 per cent. of 235 persons with anthrax, and in 3.82 per cent. a malignant pustule had developed in the bowel. In 11.91 per cent. of the cases the blood cultures were positive for several days. Rissotto (*Semana méd.*, Jan. 13, 1921).

**PROPHYLAXIS.**—The fact that French skins, since Pasteurian inoc-

ulation of attenuated living cultures has been employed in French flocks, have been found to rarely cause anthrax speaks in favor of the method.

The bodies of animals which have died of the disease should be destroyed by incineration, if possible, while diseased animals should be excluded from the field. Pasteurian vaccination has practically stamped out the disease among French herds, formol vapor, previously used, having been found not to penetrate the wool sufficiently.

Sobernheim's method of immunization consists in injecting the animal with both the bacilli and anthrax serum. This method is supposed to give the rapid immunization of the passive method, and at the same time the more lasting immunity obtained by vaccination.

Following Besredka's discovery that anthrax immunity relates to the skin and that animals can be completely immunized only by intradermal vaccination, this route of administration has been employed with excellent results.

After subcutaneous injection of anti-anthrax serum in army horses and mules during epizootic prevalence of the disease, the loss of animals amounted to 8.1 per thousand, as against only 0.45 per thousand following intradermal vaccination. Nicolas (*C. r. Soc. de biol.*, Mar. 13, 1925).

Intradermal vaccination carried out in 4092 animals. Cattle received 0.6 c.c., horses 0.4 c.c., and calves 0.2 c.c. of vaccine. The local nodule subsided in 3 or 4 days and there was no general reaction. No anthrax occurred among the vaccinated animals. Nevo-doff (*C. r. Soc. de biol.*, Jan. 29, 1926).

Persons exposed to anthrax infection should observe strict cleanliness, and may use a mask, to prevent con-

tamination through the respiratory tract.

All dressings of anthrax cases should be burned and the discharges disinfected with strong corrosive sublimate solution. As soon as vacated, the room should undergo rigid disinfection, in view of the marked resistance of anthrax spores.

Only 2 processes have been found effective for sterilizing hair as to anthrax: (1) Boiling in water at 212° F. for at least 3 hours; (2) placing in an autoclave in which a 10-inch vacuum is produced, live steam being then turned on and kept at 15 pounds pressure for 3 hours. New York Dept. of Health (Weekly Bull., Feb. 11, 1922).

**Iodine** is reliable for the disinfection of hides, and does not injure them. There are 2 general methods, vapor and wet disinfection. In the latter, the solvent used may be either water or a volatile fluid such as carbon tetrachloride or a mixture of the latter with gasoline. H. F. Smyth and E. F. Pike (Amer. Jour. of Hyg., May, 1923).

For the sterilization of shaving brushes, the writers advise a washing with **soda** followed by immersion in dilute **formaldehyde**, kept at 40 to 50° C., and a final thorough rinsing in water. O. Thomsen and V. Jensen (Hospitalstid., Oct. 15, 1924).

**TREATMENT.**—In man the disease remains localized a longer time than in animals. When it is clearly circumscribed it is possible to remove it more thoroughly. Complete **excision** of the affected part by means of the knife or **thermocautery**, and sometimes **cauterization** with **nitric acid**, are practised by some. In recent years the tendency has been rather toward the conservative measures, partly on the plea that general infection is favored by surgery.

When excision fails, the writer injects 3 or 4 syringefuls of 8 per cent. **phenol** into the edematous zone; it may effect a cure. An **ice-bag** should be applied, although some physicians have successfully used heat. He then gives **antianthrax serum**. **Salines** are given in full doses and **strychnine**,  $\frac{1}{300}$  grain (0.002 Gm.) every 4 or 5 hours. The patient should have plenty of **fresh air** and should be kept quiet. A tracheotomy tube should be kept handy in case the edema reaches the larynx. D. G. Dudley (Jour. Amer. Med. Assoc., Jan. 5, 1918).

Wide **excision en masse** of the pustule with the surrounding edematous tissues recommended, to be followed by cauterization with 10 per cent. **zinc chloride** solution. Out of 60 cases, only 2 died, and the cosmetic end-results were satisfactory. L. Conti (Policlin., May 29, 1922).

The opinion has been steadily gaining ground that the most effectual treatment for anthrax consists in the administration of **anti-anthrax serum** in large dosage. The results have been so good, when a reliable serum has been used, that they almost warrant it being grouped with the specific agents for diphtheria and tetanus. A perfected serum has been prepared under the direction of A. Eichhorn, of the Bureau of Animal Industry, Washington, and various commercial biologic laboratories supply the improved product. Out of 12 cases reported in New York City during the first 6 months of 1920, but 1 died, while in 1915, 9 out of 13 cases had succumbed.

The following details are given by J. C. Regan regarding the systemic serum treatment for anthrax: *A. In non-septicemic forms:* (1) In *mild* cases, with a small, well circumscribed lesion, little edema and little or no constitutional disturbance, the serum need not be given more often than every 12 to 24 hours, and, usually, not more than

4 injections are required, of from 40 to 50 c.c. each. The first few injections may be given intravenously; the subsequent, intramuscularly and subcutaneously. (2) In *moderate* cases, with or without definite constitutional symptoms, the serum should be given intravenously for the first 3 or 4 injections every 8 or 12 hours, in amounts of from 50 to 60 c.c. Subsequent injections are made in accordance with the progress of the case, and given intramuscularly or subcutaneously. Commonly, not more than 6 injections are required. (3) In *severe* cases, with large voluminous lesions and extensive edema, the serum should be given intravenously in doses of from 80 to 120 c.c., every 6 to 8 hours, for 5 to 6 or more injections, until the disease is controlled, when the intramuscular route can be used, the dosage diminished to 20 to 40 c.c., and the interval lengthened to 24 hours.

*B. In septicemic cases*, the injections should be given every 3 to 6 hours, intravenously, in doses of 100 to 200 c.c., and this type of treatment continued until the septicemia is terminated.

Excision is inadvisable because it may disseminate the infection. The swelling is due to the semigelatinous anthracomucin, the purpose of which is to hinder development of the bacilli, and which should consequently not be interfered with. The **serum** treatment should be intensive at first, then gradually reduced after 48 hours or if blood culture proves negative. In 13 out of 16 cases treated at the Bellevue Hospital, 40 c.c. of serum were given intravenously and 10 c.c. locally every 4 hours. All injections were preceded by a desensitizing dose. In 3 cases local injections of serum were alone given, 2 cases being given 10 c.c. every 4 hours for 5 days and the other, 10 c.c. daily for 3 days. Out of 4 septicemic cases, 3 died. The 12 other cases recovered. All cases should be considered septicemic from the start and 1 or 2 massive doses of serum given intravenously until the blood culture proves definitely negative. Serum reactions occurred in nearly all instances. H. E. Santee (Ann. of Surg., Sept., 1923).

The **local serum treatment** of anthrax has been highly recommended by Regan and employed with success by others. It is used in conjunction with the systemic serum treatment. Regan's procedure is as follows: A 2 to 5 c.c. syringe, with a fine needle, is used. The needle is inserted into the indurated border of the pustule, and is directed fairly deeply (from 2.5 to 3.5 cm.) into the subcutaneous tissues at the base of the lesion. A maximum of 10 to 12 c.c. of serum is then given, the needle being inserted at 2 or 3 points, and the serum injected so as to circumscribe the pustule. The site of injection is previously iodinated, and the operation carried out with careful aseptic technique. The injections are given once or twice in 24 hours in mild and moderate cases; in severe voluminous lesions, every 6 to 8 hours.

Six recoveries under general and local serum therapy. The procedure is to inject a total of 6 to 12 c.c. of **serum** (prepared by the Eichhorn method) at 2 or 3 points about 1 cm. outside the eschar, in the indurated zone. In the usual case 4 to 6 such injections, given once, twice or, rarely, 3 times a day, suffice. In addition, serum is given intravenously, intramuscularly and subcutaneously in a dosage ranging from 40 c.c. every 12 to 24 hours in mild cases to 200 to 300 c.c. every 3 to 6 hours intravenously in septicemic cases. The writers' total series includes 16 cases, of which all recovered but 2, who had well-developed septicemia on admission. The anthrax wound heals quickly under serum, with practically no scarring. In the 6 new cases the cultures from the lesion were positive in all but 1 case, in which incision had been carried out before admission. All cultures after the initial serum treatment were negative. J. C. and C. Regan (Amer. Jour. Med. Sci., Feb., 1924).

Under proper serum treatment, in the favorable cases, the acute inflammation disappears from the 2d to the 6th day, the eschar separates from the 12th to the 21st day, and the wound heals from the 20th to the 32d day (Regan).

**Scclavo's serum**, in use many years before the introduction of Eichhorn's serum, has been much employed in Europe and South America, and somewhat in the United States, with fairly satisfactory results.

In South America **normal beef serum** has been extensively used, with statistical results showing in large series of cases a mortality of from 6.2 to as low as 0.5 per cent. Penna, Cuenca and Kraus specify a subcutaneous dosage of 30 to 50 c.c., repeated in 12, 24 or 36 hours as required; in very severe cases the serum may be given intravenously, preferably after sterilization by heating twice for  $\frac{1}{2}$  hour at 56° C. The results from normal beef serum have not been as good elsewhere as in South America, and even some of the Argentine observers have found them inferior. An explanation offered is that local conditions govern the immunizing properties of the serum, the apparently normal animals from which serum was obtained in the Argentine having developed antibodies in their blood through ingestion of anthrax spores while at pasture on infected meadows. Another explanation is that of a non-specific protein shock reaction induced by the serum.

Koch maintained that **bichloride of mercury** is a most effective poison for the anthrax bacilli, being capable of killing them when used as dilute as 1 part to 300,000 of water. Injections of 1:100 bichloride may be made

in and around the affected part. **Phenol** in 2 to 8 per cent. solutions has also been used.

A method employed by Sassi consists simply in the injection of 5 drops of **phenol** in 3 places about the lesion, *i.e.*, 15 drops in all, at one dose. This may be repeated the same day.

**Arsphenamin** and **neoarsphenamin** have been tried, apparently with favorable results. In anthrax bacteremia and internal anthrax Kolmer dissolves 0.9 Gm. of neoarsphenamin in 100 c.c. of sterile saline solution, adds 100 c.c. of antianthrax serum, and injects the mixture intravenously.

A single injection of 0.45 to 0.6 Gm. of **neoarsphenamin** may cure recent cases of anthrax. Chill, fever and sweating occur on the same day, after which the temperature declines. This decline may not occur for 3 or 4 days, however, in severe cases, in which event the treatment is repeated 2 or 3 times at 2-day intervals. O. Grasser (Wein. klin. Woch., Mar. 13, 1924).

The fact that experiments have shown that **ippecacuanha** added to tubes containing 5 c.c. of broth invariably inhibit any anthrax bacilli present, has suggested the use of this drug as a remedy.

In 18 consecutive cases of anthrax without a death, the writer surrounded the pustule with a ring of injections of 5 per cent. **phenol solution**, deep into the subcutaneous tissue, from 40 to 80 minims ( $2\frac{1}{2}$  to 5 c.c.), in all, being employed. This is repeated each day for 3 or 4 days, when a **fomentation of powdered ipecac** (about 1 dram—4 Gm.—moistened with a little warm water) is applied and covered with oiled silk. The fomentation is repeated daily until the black slough begins to separate, after which **wet boric acid dressings** are used to expedite healing. Phillips. (China Med. Jour., May, 1915).

In a case of anthrax septicemia, seemingly moribund, following a kick on the hand by a cow, intravenous injection of 20 c.c. of a 1 per cent. solution of **argochrome** was followed in 4 hours by general improvement, and upon repetition 2 days later, resulted in recovery. Two other cases also successfully treated with this agent, chemically methylene-blue silver. Methylene-blue acts selectively on the anthrax bacillus E. Baumann (Klin. Woch., Dec. 9, 1922).

BASIL R. BELTRAN,  
Philadelphia.

**ANTIMONY.**—The only official salt of antimony is *antimonii et potassii tartras*—tartar emetic, tartrated antimony, or stibiated tartar [ $2\text{K}(\text{SbO})\text{C}_4\text{H}_4\text{O}_6 + \text{H}_2\text{O}$ ].

**PROPERTIES.**—Tartar emetic occurs in the form of colorless, transparent crystals, which become opaque on exposure to the air, or as a white powder. It is without odor, but possesses a sweetish and at the same time acrid, metallic taste. It is soluble in 12 parts of water at  $25^\circ\text{C}$ ., in 3 parts of boiling water, and in 20 parts of glycerin, but is insoluble in alcohol.

**DOSE.**—The dose of antimony and potassium tartrate ranges from  $\frac{1}{30}$  grain (0.002 Gm.) to 1 grain (0.065 Gm.), the average expectorant dose being  $\frac{1}{10}$  grain (0.0065 Gm.) and the emetic dose  $\frac{1}{2}$  grain (0.032 Gm.).

**PREPARATIONS.**—The following official preparations, exclusive of the salt itself, contain tartar emetic:

*Syrupus scille compositus* (compound syrup of squill; Coxe's hive syrup), which, in addition to squill and senega, contains 0.2 per cent. of tartar emetic; dose, 30 minims (2 c.c., containing  $\frac{1}{16}$  grain, or 0.004 Gm., of the antimony salt).

*Mistura glycyrrhizæ composita* (compound licorice mixture; brown mixture), containing extract of licorice, camphorated tincture of opium, sweet spirit of niter, and 0.024 per cent. of tartar emetic; dose, 1 to 2 fluidrams (4 to 8 c.c., containing approximately  $\frac{1}{64}$  to  $\frac{1}{32}$  grain, or 0.001 to 0.002 Gm., of tartar emetic).

Wine of antimony was formerly official as a 0.4 per cent. solution of tartar emetic in white wine; dose, 15 minims (1 c.c., containing  $\frac{1}{16}$  grain, or 0.004 Gm., of tartar emetic).

**MODES OF ADMINISTRATION.**—Tartar emetic is best administered in solution, with its metallic taste disguised by some flavoring agent, such as syrup of orange peel. The more dilute the solution given, the greater likelihood of the production of a cathartic effect. Tartar emetic, and some unofficial antimony compounds, are also sometimes given intravenously.

**INCOMPATIBILITIES.**—Tannic acid and salts of silver and lead precipitate antimony compounds.

**CONTRAINDICATIONS.**—In all cases which show a tendency to cardiovascular depression or marked general adynamia, antimony compounds should be avoided. In the aged, as well as in children, they should be used only with circumspection, and in small doses.

**PHYSIOLOGICAL ACTION.**—

**Local Effects.**—Tartar emetic exerts an irritating effect when applied locally. If left in contact with the skin for several days it causes local hyperemia and pain, soon followed by an eruption of small papules, arising from the dermal glands and hair follicles. The lesions soon become transformed into vesicles and

ultimately into large pustules. Considerable local pain is likely to be present. If the application be not discontinued, ulceration and sloughing of the superficial tissues may ensue. The irritation caused by tartar emetic is due not to the double salt itself, but to simple salts of antimony formed through the decomposition of the double compound by the acid skin secretions (Sollmann).

**General Effects.**—*Nervous System.*—Small single doses of tartar emetic do not exert any appreciable nervous effect. Large amounts diminish or abolish sensation by depressing the sensory columns of the spinal cord. Although the motor side of the cord may also be to a certain extent depressed, this effect is secondary to that on the sensory portion, as shown by the fact, recorded by certain experimenters, that voluntary movements may occur in frogs poisoned with antimony after the spinal reflexes have been paralyzed. In man it is not known how much of the spinal depressant effect is due to direct action of the drug on the nerve-cells, and how much to circulatory disturbances.

*Circulation.*—Antimony is a direct depressant to the heart. Even moderate doses exhibit eventually a tendency to slow and weaken the pulse, though the preliminary emetic action is generally attended with a temporary increase in the rate. The blood-pressure shows a gradual fall under antimony, partly owing to the cardiac weakening, but in considerable measure, it is believed, because of vascular dilatation. It appears to be established that antimony depresses directly the muscular walls of the vessels, as it does the cardiac

musculature. Whether depression of the vasomotor center is likewise a factor in the fall of blood-pressure has not as yet been definitely ascertained. According to Sollmann, who assimilates the circulatory effects of antimony to those of arsenic, the capillary vessels are also paralyzed by this drug, their walls becoming more permeable,—a fact which accounts for the diarrhea after full doses, further favoring a reduction in the blood-pressure. Circulatory depression under antimony compounds may also be produced as a sequela to the emesis.

*Respiration.*—The respiratory center is but little influenced by antimony except in cases of poisoning, when it is manifestly depressed. In the early stages, and with small doses, various relatively unimportant changes in the breathing rate take place indirectly as a result of nausea and circulatory depression.

*Alimentary Tract.*—Taken internally in full doses, tartar emetic induces nausea and vomiting, an effect generally considered to be due chiefly, if not wholly, to irritation of the gastric mucosa. These symptoms also appear upon hypodermic or intravenous injection of the drug, but larger doses must be used in order to produce them than are required upon oral administration. Ordinary doses of tartar emetic do not seem to alter the appearance of the gastrointestinal mucous membranes; larger amounts induce marked congestion of the membranes and exfoliatory diarrhea, as in arsenic poisoning or Asiatic cholera. The irritation caused by tartar emetic in the stomach has been ascribed, like that produced when it is applied exter-



nally, to decomposition of the double salt into a simple antimony salt by the acid of the gastric juice; this probably does not account wholly, however, for the irritant effect, as similar irritation is produced by the drug in the intestine, the juices of which are alkaline in reaction.

The vomiting induced by antimony compounds is accompanied, like that resulting from the ingestion of other emetics, by free perspiration, an increased flow of saliva, and general depression.

Large doses of antimony also cause intestinal irritation, with the production of a more or less profuse and watery diarrhea, often accompanied by colic.

*Secretions.*—Antimony compounds exert no direct effect on the secreting organs. The nauseant effect of small doses, however, leads indirectly to an increase in the salivary discharge, perspiration, and mucous secretions of the respiratory tract. Variable and relatively insignificant alterations may occur in the secretion of urine, which may be either increased or diminished.

*Temperature.*—The temperature is not appreciably influenced by ordinary doses of antimony. After doses sufficient to produce violent emesis, the temperature of the extremities may be distinctly lowered (Ackermann). Toxic doses cause a pronounced general hypothermia.

**ABSORPTION AND ELIMINATION.**—Antimony is rather promptly absorbed from the gastrointestinal mucous membranes, though not with quite the same rapidity as arsenic. It is also readily absorbed from abraded surfaces; cases of fatal poisoning have occurred in this way.

After absorption the metal tends to accumulate in the liver. Its paths of excretion lie through the kidneys, alimentary tract, and in less degree through the respiratory mucous membranes, the salivary and mammary glands, and the skin.

**UNTOWARD EFFECTS AND ACUTE POISONING.**—Excessive doses of antimony compounds produce an exaggeration of the ordinary emetic effect. Vomiting is violent and persistent, may become bloody, and is attended with intense prostration. There is marked thirst, and a sense of constriction in the throat. Pains in the abdomen and diarrhea also occur, the fecal discharges becoming serous, *i.e.*, of the choleraic type. Cramp-like pains in the extremities may occur. The bronchial secretions may be greatly increased. Symptoms of collapse soon make their appearance. The pulse, at first often accelerated, becomes slow and feeble. The respiration is likewise depressed, the skin bathed with perspiration and more or less cyanosed, the muscles relaxed, and the temperature lowered. The urine may be increased at first; later it is scanty, albuminous, and perhaps bloody. A period of stupor, terminating with feeble convulsive movements, may precede death. The period required for the completion of fatal poisonous effects ranges from one hour—the shortest lethal period on record—to several days. In patients still alive on the third, fourth, or fifth day, a pustular eruption may appear.

In rare cases the gastrointestinal symptoms, especially the vomiting, are said to be totally absent, collapse and delirium being the more prominent features.

The lethal dose of antimony cannot be definitely stated. One patient is said to have succumbed to 2 grains (0.13 Gm.) of tartar emetic, while doses of several hundred grains have been recovered from, doubtless in part owing to the thorough emesis produced. According to Reese, 20 to 40 grains (1.3 to 2.6 Gm.) represent about the fatal dose. Even relatively small doses of antimony compounds may prove harmful in conditions associated with cardiac weakness. The direct depressing action of the drug on the myocardium easily leads to a slowing and weakening of the heart action, but a reflex inhibitory effect through the vagus may also be considered in part responsible for cardiac arrest under antimony (Pouchet). The combined cardiac and vasomotor depression in cases of poisoning leads to a marked fall of blood-pressure and hyperemia of the venous side of the circulatory system.

The changes found *post mortem* consist chiefly of intense hyperemia of the gastrointestinal tract and other viscera, especially the liver and lungs. The mucous membranes of the stomach, bowels, and respiratory tract are usually reddened and covered with blackish secretions. The lungs may show points of hemorrhage, as well as areas of emphysema or atelectasis. The liver is softened, and the brain is likely to present apoplectic foci. The blood is said to remain uncoagulated. In some cases—probably those with a rapid fatal ending—the gastrointestinal changes have been wanting.

**TREATMENT OF ACUTE ANTIMONIAL POISONING.**—Tannic acid, most easily obtainable in the form of tea, should be freely given to precipitate the antimony still in

the stomach. If vomiting is present the precipitated tannate will be spontaneously ejected, especially if mucilaginous fluids are administered to assist in the clearing out; if there is no vomiting at the time, the precipitate should be washed from the stomach with a **stomach tube**. Soluble **magnesium** or **calcium salts** may also be used as precipitants. A purge may be given to remove the metal as promptly as possible from the intestinal tract. Symptomatic relief is afforded by **opium** or **morphine**. Collapse should be combated with **strychnine**, **caffeine**, **digitalis**, **camphor**, etc., and the application of **external heat**. **Demulcent drinks** are useful to soothe the irritated mucous membranes during recovery.

A patient was improving under treatment with tartar emetic for bilharziasis, when suddenly, after injection of 0.09 Gm. ( $1\frac{1}{2}$  grains) of the drug, he developed chills and contractions and pains in the muscles, similar to those of severe malaria. The temperature rose to 104° F., with vomiting.

Under **rest**, **rubbing with camphorated oil** and **hot drinks**, a **purge** and an **emetic**, he recovered. The pain and soreness of the muscles continued for several days. Rísquez (Gaceta med. de Caracas, Mar. 31, 1920).

**CHRONIC POISONING.**—Chronic antimonial poisoning is comparatively rare. The symptoms in many respects resemble those of acute poisoning. Meierhofer and Nobling experimentally took 1 mg. ( $\frac{1}{60}$  grain) of tartar emetic daily, gradually increased to 1 cg. ( $\frac{1}{6}$  grain), for two weeks. The early symptoms noted included: sensation of weakness in the limbs and pains in the joints, chilliness, salivation, thirst, inner feeling of warmth, som-

nolence, nightmares, frequent and irregular pulse, vertigo, pallor. Later there appeared anorexia, nausea, colicky pains, dysphagia, dyspnea, precordial pain, diarrhea alternating with constipation, polydipsia resulting in diuresis, weak and slow heart action, hepatic engorgement and pain, prostration, albuminuria, and a loss in body weight amounting to 3½ kg. (over 7 pounds). Two months were required for complete disappearance of the phenomena of intoxication (Pouchet). Pustular eruptions are also sometimes observed after continued use of antimony preparations.

**THERAPEUTICS.—As an Expectorant.**—Antimony compounds are still used to a certain extent for the purpose of increasing the secretions, especially the discharge of mucus in the respiratory passages in catarrhal inflammations associated with excessive local dryness and cough. The outpouring of fluid produced is a result of the nauseant effect of the drug; in this respect antimony is preferable to any other metal in that only about one-tenth the emetic dose is required to induce nausea (Sollmann). The dose of tartar emetic as expectorant in the early stages of **acute bronchitis** or **laryngitis** in adults is about  $\frac{1}{10}$  grain (0.0065 Gm.). In the later stages, when free secretion is present, antimony is no longer suitable. It is not infrequently administered in the form of the official compound syrup of squills, dose 30 minims (2 c.c.); or the wine of antimony, dose 15 minims (1 c.c.). Other preparations, used chiefly on the continent of Europe, include the so-called "kermes mineral," or sulphurated antimony,—a mixture of the

oxide and sulphide of antimony with acid antimonite of sodium,—dose 1 to 4 grains (0.065 to 0.25 Gm.), and the white oxide of antimony, or acid potassium antimoniate, used in even larger doses. While the last-named preparations are credited with exerting a milder, more gradual effect than tartar emetic, they have the disadvantage of being insoluble in water and depending in part for their absorption upon the hydrochloric acid present in the alimentary tract; their absorption is, therefore, subject to variation with a resulting probability either of inefficiency of the drug or of excessive action and vomiting.

In view of the possible depressing effect of antimony compounds upon the circulation it is perhaps advisable to combine some cardiovascular stimulant with them. Thus, Pouchet writes the following:—

R *White oxide of antimony* ..... 7½ grs. (0.50 Gm.).  
*Tincture of digitalis* ..... 6 grs. (0.40 c.c.).  
*Syrup of orange flower* ..... 2 fl. oz. (60 c.c.).

M. Sig.: One tablespoonful every two hours.

In the later stages of catarrhal inflammations, when free secretion is present, antimony compounds are no longer advisable.

Antimony and potassium tartrate is a remedy of great value. To obtain free secretion from the mucous surfaces and the skin, antimony remains pre-eminent. It should always be prescribed in small doses given frequently. Only by this means can its full effect be obtained without danger of giving rise to depression. In **bronchial catarrh** and **bronchitis** there is no drug to take its place. Great severity in the attack is no bar to the use of the drug. In the early stage of **bronchopneumonia** in children it is of undoubted value, being

most useful at the period when the consolidation is still in patches. Belladonna is also of value at the same period, and the two remedies may be combined. **Laryngismus stridulus** is another disease in which antimony is of great benefit; it should be given as wine of antimony in doses of 15 to 20 drops (0.9 to 1.2 c.c.), so as to induce a slight feeling of nausea. Smith (Brit. Med. Jour., Feb. 29, 1908).

**As a Diaphoretic.**—Antimony compounds, likewise by reason of their nauseant effect, are capable of producing sweating, and were formerly so used to a considerable extent. In view of the fact, however, that other more efficient and less depressing diaphoretics are available, there appears to be practically no occasion for the use of antimony in this direction.

**As an Emetic.**—Conditions are much the same in respect to the use of antimony as an emetic. The full doses—such as  $\frac{1}{2}$  grain (0.03 Gm.) of tartar emetic—required to produce emesis are particularly likely to bring on unwelcome cardiovascular and general systemic depression. Further, the drug has the disadvantage of acting more slowly than apomorphine, zinc or copper sulphate, and ipecacuanha. In cases of **poisoning** unattended by cardiovascular depression, the use of a combination of ipecac with tartar emetic is sometimes recommended, the former drug supplying the promptness of action which the antimony compound lacks, while the latter adds to the effectiveness of the emesis and prolongs it.

Smith found the wine of antimony in doses of 1 or 2 minims (0.06 or 0.12 c.c.) a useful addition to the prescription in cases of gastric derangement. It acts, in his opinion,

on the principle that all nauseating medicines, given in minute doses, lose their irritating properties and become gastric sedatives.

**As a Cardiovascular Sedative.**—At the start of acute infections, particularly in **pneumonia**, tartar emetic was formerly administered in large doses for the purpose of lowering vascular tension and thereby antagonizing congestion of the affected part. It was also claimed that the sudden more or less forcible movements attending the act of vomiting, by exerting mechanical pressure upon the lungs, favored the circulation of blood in the lung-vessels and forestalled stasis. In addition, the purgative and nervous sedative effects were also regarded with much favor. More recently it has become quite clear that these supposed advantages are more than offset by the almost universal depressant tendency of the drug. The apparent state of tolerance to antimony established by repeated use of large doses has been shown to amount merely to a condition of lowered tone of the nervous system.

**As a Parasiticide.**—This is at present the most important use of the antimony compounds, but it is limited to certain forms of infection, chiefly those due to organisms belonging to the lowest classes of the animal kingdom. The efficacy of antimony in this direction first came to light in respect of **trypanosomiasis**, in which it has given comparatively good results. It has been administered in the form of tartar emetic, by the mouth or by intravenous, intramuscular or subcutaneous injection. The latter 2 methods, however, seem impracticable owing to the

severity of the local reaction. The intravenous method is decidedly the most efficient, and is generally availed of both in trypanosomiasis and other infections, and both as regards tartar emetic and other antimony compounds, more recently brought into use. The intravenous dose of tartar emetic ranges from  $\frac{1}{6}$  to 2 grains (0.01 to 0.12 Gm.), usually administered in 1 per cent. strength in normal salt solution. According to Christopherson, a total of 60 grains (4 Gm.) or more of potassium or sodium antimony tartrate is required in repeated courses to cure trypanosomiasis. In bilharziasis, 20 to 30 grains (1.3 to 2 Gm.) are necessary, as a rule, while in leishmaniasis of the skin (kala-azar), 5 to 8 grains (0.3 to 0.5 Gm.) may suffice. Antimony compounds are also used intravenously in **granuloma inguinale**, with considerable success.

In **malarial remittent fever**, Frances recommended the use of tartar emetic internally in cases with highly congested face and violent headache.

Tartar emetic by vein found effectual in various infections, including **chronic malaria**. Benjamins (Nederl. Tijdsch. v. Geneesk., Jan. 1, 1921).

Ammonium antimonyl tartrate is the least toxic of all the antimonyl tartrates used, and is of marked value in **kala-azar**. Its antimony content is high. A much safer antimonial for use in kala-azar than tartar emetic or other antimonyl tartrates is, however, *urea stibamine*, a new organic aromatic antimonial. Symptoms, such as vomiting and purging, are much less marked after intravenous injection of an effective dose of urea stibamine (0.25 Gm.—4 grains) than after such a dose of tartar emetic or sodium antimonyl tartrate (0.12 Gm.—2 grains). In animal experiments, the pathologic changes following toxic doses of anti-

monials were most marked in the lungs, kidneys, liver, pituitary and suprarenals, consisting chiefly of parenchymatous hemorrhages and destruction of the cells. Brahmachari (Indian Jour. of Med. Res., Oct., 1922).

Two new antimony compounds for intravenous use described, *viz.*, *sodium antimony thioglycollate* and the *triamide of antimony thioglycollic acid*. The following drawbacks of tartar emetic are stated to be overcome in these products: Questionable stability when heated for sterilization; production of alarming symptoms and an occasional death; bone aches, dyspnea, etc. The new drugs also showed lower toxicity and greater therapeutic value. The first is a white powder, very soluble, of the formula  $(\text{CH}_2\text{S})_2\text{SbCOO}\cdot\text{COO}\cdot\text{Na}$ , and containing 37.17 per cent. of antimony. It can be sterilized by boiling without chemical change other than the separation of a little antimony sulphide, which can be filtered off under sterile conditions. The second compound occurs in white, glistening plates, soluble 1:200 in water, of the formula  $\text{Sb}(\text{S}\cdot\text{CH}_2\text{CONH}_2)_3$  and containing 30.77 per cent. of antimony. It is much more soluble in boiling water, and on sterilization behaves like the first compound. The dosage of the second drug is one 20 c.c. ampule of a 0.4 per cent. solution. The first drug is used in a 20 c.c. ampule of a 0.5 per cent. solution or 10 c.c. of a 1 per cent. solution. In 7 cases of **granuloma inguinale**, daily intravenous injections were given with excellent results and no general, local or vascular irritation. There is some evidence of the feasibility of injecting these drugs likewise subcutaneously or intramuscularly. A. Randall (Amer. Jour. Med. Sci., Nov., 1924).

Evidences of hypersensitivity, after non-toxic doses, are frequently exhibited by patients receiving a prolonged course of intravenous antimony injections. This may be due to an alteration of protein metabolism and in extreme cases may resemble true protein shock. Degeneration and destruction of the liver and kidney

parenchyma were found in a man who died from an accidental mistake in dosage in intravenous antimony injection. In rabbits given lethal injections, the changes noted were dilatation of the capillaries, effusions in serous cavities, hemorrhages into the lungs and spleen, and retention of urine, in addition to degeneration of the hepatic cells and, less markedly, of the renal tubules. Christopherson and Gloyne (Lancet, Jan. 30, 1926).

In certain skin diseases, including eczema and other inflammatory states, antimony in small doses has been recommended as a substitute for arsenic.

In anemia antimony has also been praised as an arsenic substitute. According to Montemagno, it increases the number of red cells and percentage of hemoglobin, and also enhances the resistance of the red cells, as does arsenic. The improvement in the blood after antimony persists for some time after it has been discontinued. Large doses, however, produce hemolysis.

Externally, antimony compounds have been applied to the skin to obtain prolonged counterirritant effects. Their tendency to cause eruptions and even destroy the tissues locally constitutes a marked disadvantage of its local use.

Unna recommended a solution of chloride of antimony (about 30 per cent.) as a local remedy in lupus, claiming that it had a selective affinity for the tuberculous nodules. Beneficial effects in other cutaneous diseases, including psoriasis, have also been reported.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

**ANTIPYRIN.**—This substance, official in the U. S. Pharmacopœia as *Antipyrina*, and in the British Pharmacopœia as *Phenazonum*, is an organic base obtained by the condensation of acetoacetic ether with phenylhydrazine, and methylation of the compound thus produced by means of methyl iodide. The constitution of antipyrin is expressed by the chemically descriptive term Phenylidimethylpyrazolon, and its formula is  $(C_6H_5)_2N.N(CH_3).C(CH_3):CH.CO$ . It is also sometimes known as Analgesin.

**PROPERTIES.**—Antipyrin occurs as a fine, white, crystalline powder. It has no odor, but is slightly bitter in taste. It is distinguished from the other ordinary coal-tar antipyretics—acetanilide and acetphenetidin—by its ready solubility in water, 1 part of antipyrin dissolving in less than an equal weight of water. It is soluble in 1 to 2 parts of alcohol, 1 to 2 parts of chloroform, and 30 to 50 parts of ether, according to the temperature.

**DOSE.**—The dose of antipyrin for adults is 5 to 10 grains (0.3 to 0.6 Gm.); 15-grain or even larger doses were formerly often given, but in late years it has been recognized that such dosage is excessive and unnecessary. Doses larger than  $7\frac{1}{2}$  grains (0.5 Gm.) cannot be considered safe, and this dose should not be repeated for four hours (Mayor). To children, who bear the drug well, as many grains of antipyrin may be given as there are years of age, until the adult dose is reached.

Out of 150 physicians using antipyrin, only 23, or 15.3 per cent., exceeded a dose of 10 grains (0.6 Gm.), while 66, or 44 per cent., never exceeded a dose

of 5 grains (0.3 Gm.); 109, or 72.6 per cent., employed 5 grains (0.3 Gm.) or less as a minimum dose. Kehler, Morgan, and Rupp (U. S. Dept. of Agricul., Bureau of Chemistry, Bull. No. 126, July 3, 1909).

**MODES OF ADMINISTRATION.**—Antipyrin may be given either in powder form or dissolved in water. The latter method is preferable, as the local irritant effect of the drug on the gastric mucosa is thereby minimized. If it cannot be taken except in a capsule, the patient should take a quarter- or half- glassful of Vichy water immediately after (Clement). Whenever practicable, the drug should be taken with or after meals. The bicarbonates of sodium or potassium may be combined with antipyrin with advantage, as they tend to neutralize, through their alkalinity, the effects of any products of decomposition which may be formed in the stomach by the action of the gastric juice on the drug. Brissemoret recommends the following plan of administering antipyrin: A tablespoonful of a mixture consisting of antipyrin, 4 Gm. (1 dram); sodium bicarbonate, 2 Gm. ( $\frac{1}{2}$  dram); simple syrup, 15 Gm. (4 drams), and distilled water, 45 Gm. ( $1\frac{1}{2}$  ounces), is first taken, and is at once followed by a like amount of the following: Citric acid, 2 Gm. ( $\frac{1}{2}$  dram); distilled water, 50 Gm. ( $1\frac{3}{4}$  ounces), and syrup of limes, 15 Gm. (4 drams). Carbon dioxide is liberated in the stomach, mitigating the local irritant effect of antipyrin, and potassium carbonate is subsequently formed from the citrate, counteracting any deleterious effect which the drug may tend to exert on the blood. A simpler plan for giving antipyrin in an effervescent preparation is to dissolve the

drug in some water containing carbonates, such as Vichy, and add citric acid. Coffee has been recommended by Batterbury as a good vehicle for antipyrin; its taste is thereby almost entirely disguised.

**INCOMPATIBLES.**—Antipyrin is incompatible with many substances. As already stated, it is an organic base, and, therefore, reacts with the whole series of alkaloidal precipitants. It is thrown down from concentrated solutions by pure phenol, by tannic acid and drugs rich in it (catechu or gambir, kino, hamamelis, cinchona, rheum, rose leaves, uva ursi); by solutions of salts of mercury, lead, and copper; by compounds of arsenic and antimony, by tincture of iodine, and by alkalies. When rubbed up with chloral hydrate or with sodium salicylate it forms an oily liquid.

It is decomposed by betanaphthol and potassium permanganate, and when combined with sodium bicarbonate is said to disengage the odor of ether. Nitrites, including spirits of nitrous ether, cause a green color to develop when added to dilute solutions of antipyrin, owing to the formation of a nitrosoantipyrin; in concentrated solutions a green crystalline precipitate is formed. Ferric chloride colors antipyrin solutions red; ferrous phosphate, yellow-brown; ammonia alum, dark yellow; hydrocyanic acid, yellow; nitric acid, pale yellow, and fuming nitric acid, green. Combination of antipyrin with calomel has been warned against, in view of the possible formation of a dangerous amount of corrosive sublimate (Werner, Robinson). Especially is such a combination with the further addition of sodium bicarbonate to be avoided.

If a prescription calling for 2 grains (0.13 Gm.) of calomel, 6 grains (0.39 Gm.) of antipyrin, and 12 grains (0.77 Gm.) of bicarbonate be taken *in toto* by a patient, that patient would receive a soluble mercury salt equal to  $\frac{1}{3}$  or  $\frac{1}{2}$  grain (0.021 or 0.032 Gm.) of corrosive sublimate. If administered in capsules the danger would be somewhat less, as the gastric acidity would tend to neutralize the sodium bicarbonate, on the presence of which the reaction depends. Report from Association Laboratory (Jour. Amer. Med. Assoc., Jan. 28, 1911).

Antipyrin is also incompatible with benzoates, orthoform, resorcin, thymol, pyrogallol, ethyl carbamate, and chromic acid.

The precipitation of antipyrin in the presence of iodine has been suggested by Maragliano as a test for minute quantities of the drug; 5 drops (0.3 c.c.) of Lugol's solution added to 6 c.c. (97 minims) of acidified urine will cause a reddish precipitate to form.

**CONTRAINDICATIONS.**—In patients with greatly weakened hearts or marked general enfeeblement, and in persons of advanced age, antipyrin is relatively unsafe, owing to the possibility of its inducing cardiac depression, as well as lowering the blood-pressure through excessive vascular dilatation. According to Huchard, antipyrin is contraindicated in all cases of renal disease, since its elimination is then interfered with, and unexpected toxic effects may develop. More especially does this hold in febrile states—pneumonia, typhoid fever, tuberculosis—complicated by nephritis. Spanoudis found persons suffering from erysipelas peculiarly susceptible to antipyrin; it usually caused anuria and a profound fall of temperature.

## PHYSIOLOGICAL ACTION. —

**As Antipyretic.**—Antipyrin was introduced into medicine as a reducer of fever in 1884, and was soon found to be more effective and less dangerous than any other drug previously discovered. Doses of 10 or 15 grains (0.6 to 1.0 Gm.) produce, provided pyrexia be present at the time, a fall of temperature of from 1° to 5° F. (0.5° to 2.8° C.). According to Manquat, this effect begins one-half hour after the ingestion of the drug; in about four hours (the period varying according to the cause of the febrile process) the temperature commences to rise again.

The cause of the antipyretic effect of antipyrin has given rise to many investigations and discussions—by no means always concordant. In experimental animals, as in man, a reduction of temperature takes place—when small (therapeutic) doses are used—only in the presence of pyrexia, the normal temperature being uninfluenced. Massive (poisonous) doses are required to produce a like effect under normal conditions.

In the calorimetric experiments of Wood, Reichert, and Hare, dogs rendered febrile by injections of pepsin showed, under the influence of antipyrin, a decrease in both heat production and heat dissipation. The former effect usually exceeded the latter; hence, the body temperature fell. Destrée obtained similar results. Cerna and Carter, on the other hand, witnessed a pronounced increase in heat dissipation in addition to the diminution in heat production. According to Gottlieb, the reduction of temperature is due exclusively to increased heat dissipation, heat production remaining unaffected; this view



is, however, at variance with the accepted theory. As for the portion of the organism acted upon in the production of the antipyretic effect, evidence seems to point to the basal ganglia of the brain, and in particular to the region of the corpus striatum. The experiments of Sawadowski showed that, if the connections of these nerve-centers with lower nervous structures are cut, neither the coal-tar drugs nor injections of fever-producing substances cause any change in the temperature, whereas, if their superior connections are severed, the usual characteristic effects appear. In recognition of this fact it has been generally considered that the action of antipyrin takes place through the heat-regulating centers located in the portion of the brain already mentioned. The formation of body heat is held to be influenced by the control over muscular activity vested in these centers, while the output or dissipation of heat is altered through similarly regulated changes in the peripheral blood-vessels. Diminished muscular activity leads to lessened heat production, whereas dilatation of the peripheral vessels leads to increased heat loss through exposure of a greater amount of blood to the cooling influence of the surrounding air and increased evaporation of sweat. In agreement with this view as to the mode of action of antipyrin (at least with respect to heat dissipation) is the fact that often, clinically, the fall in temperature is accompanied by more or less profuse sweating, seen first about the forehead or neck, later upon the chest and face. The rise of temperature, taking place as the effect of the drug wears off, is not uncommonly at-

tended with chilly sensations and shivering. Sweating is generally considered to be more marked after the use of antipyrin than after acetanilide or acetphenetidin. It has been advised that this effect be antagonized with atropine; under these circumstances we should expect, however, the antipyretic effect to be interfered with.

The cerebrum and corpus striatum were removed from 18 rabbits. In 9, a subnormal body temperature resulted. The remaining 9 behaved essentially like normal animals. The hypopyrexia animals showed signs of collapse, asymmetrical muscular disturbances, peripheral vasoconstriction and slow respiration. Their temperature condition was not due to cold, starvation or hemorrhage, but to a disturbance of central heat regulation, probably seated chiefly in the corpus striatum. When given 0.1 to 0.4 Gm. (per kilo) of antipyrin they showed a definite rise in temperature rather than a fall, and a conspicuous absence of the vasodilation usually seen after the drug, as well as of the hyperpnea which would be expected from the larger doses within this range. Barbour and Deming (*Jour. of Pharmacol. and Exper. Therap.*, Nov., 1913).

Of late some doubt has arisen as to the actual existence of specific heat-regulating centers. If they do not exist, the drug may be presumed to act at least partly by depressing the center which controls the skin vessels.

**Action as Analgesic.**—The mode of action of antipyrin in relieving pain is still somewhat uncertain. The fact that this drug, in common with other coal-tar antipyretics, sometimes causes more or less drowsiness while exerting its effect would seem to indicate the presence of some sedative action on the nerve-centers. In-

deed, one view hitherto prominently entertained has been that the drug depressed in particular the sensory cells located in the thalamic region. The more recent studies, however, have made it seem probable that intracranial vasomotor changes are at least partly responsible for the analgesia.

Wiechowski, in 1902, performed experiments the results of which supported this conception, and, in 1909, Weber, with the aid of an improved experimental method, showed quite clearly that antipyrin, administered to animals by intravenous injection, caused, after brief preliminary dilatation, prolonged constriction of the intracranial vessels. Taking for granted the fact that similar results will obtain upon ingestion of antipyrin in man, it seems reasonable to presume that, at least in the relief of headache, antipyrin acts by inducing intracranial vasoconstriction.

The effects of antipyrin on the nervous system as a whole may be described briefly as follows: There occurs at first a mild degree of narcosis, betokened by slight somnolence, diminished reflex excitability, and lessened sensibility to pain. (Even before this, according to Pouchet, there may appear, with full doses, a brief period of excitation, attended, in man, with increased mental activity, loss of fatigue sensations, and even, occasionally, a species of dreaminess or actual "intoxication.") Succeeding the period of depression appears a stage characterized especially by exaggerated reflex response. If the dose be large enough, convulsive movements even appear, which are believed to be due to excitation both of the lower brain-centers and spinal cord,

since either clonic or tonic spasms—the former typically bulbar and the latter strychniform—may predominate. Finally, there occurs a stage of general motor paralysis and anesthesia, due to depression of the entire central nervous system by the drug.

The peripheral nerves, especially the sensory, are depressed by antipyrin when it is applied to exposed nerve-trunks or taken internally in large amounts. It is considered extremely doubtful, however, whether antipyrin in the doses employed in therapeutics can exert any noteworthy portion of its analgesic effect in this manner; the central nervous effects appear always to predominate over the peripheral.

The respiratory center in the medulla is apparently at first stimulated by antipyrin, the rate of respiration being increased. Later, with poisonous doses, there occurs paralysis of this center.

**Action on the Circulation.**—Antipyrin in moderate doses has been shown to cause a rise in the blood-pressure. With toxic doses the rise is soon followed by a pronounced fall. The primary rise is believed to be due largely to direct cardiac stimulation; but vasomotor changes are also perhaps involved. According to Gley and Caravias, antipyrin causes, in addition to dilatation of the peripheral vessels, constriction of the vessels innervated by the splanchnics, the net result being a rise in the general blood-pressure. The larger the dose, the more marked are both of these effects. With large doses, in addition, cardiac slowing and enfeeblement begin to appear, the blood-pressure, however, varying but little. Finally, under toxic doses both vasomotor centers and heart become pro-

gressively paralyzed, and a marked secondary fall of blood-pressure is seen (Pouchet).

On the blood antipyrin, even in large amounts, exerts practically no deleterious action—a feature distinguishing this drug both from acetanilide and, to a certain extent, from acetphenetidin. Though Lépine claimed to have observed methemoglobinemia in antipyrin poisoning, many authors seem disposed to deny antipyrin any methemoglobin-forming power. Lépine's opinion, however, is far more reliable. According to Sollmann, medium-sized doses of antipyrin merely render the oxygen of the oxyhemoglobin less labile—an effect doubtless sufficient to account, at least in part, for the cyanosis sometimes observed after the use of this drug.

**Action on Secretions.**—Certain secretory functions are interfered with by antipyrin (Pouchet). The renal vasoconstriction produced by the drug may reduce the flow of urine—a fact emphasized by Huchard. The sweat secretion may, however, so increase as to make up, to a certain extent, for the deficiency of renal elimination. The mammary secretion, according to Pouchet, is greatly reduced by antipyrin.

**Action on Metabolism.**—Antipyrin used in moderately large amounts has been shown by Umbach, Robin, and other investigators to lessen the metabolism of nitrogenous compounds in man. The urinary elimination of urea in particular is diminished; that of uric acid, on the contrary, may remain unaltered or be increased. Incompletely oxidized sulphur and phosphorus compounds exhibit an increase, another evidence of the fact that the drug hinders oxidation and catabolic changes in general.

Lépine showed that antipyrin led to a diminished consumption of sugar in the capillaries and lessened glycogen transformation. While these statements represent the prevailing view as to the action of antipyrin on metabolism, it must be stated that in certain experiments, especially those of Crolas and Hugounenq and of Cazeneuve, which were carried out in dogs, the elimination of urea was sometimes found to be increased instead of diminished, and that certain authors are disposed, therefore, to consider the question as not yet having been definitely settled, or, like Cushny, to accord but little significance to the effects of antipyrin in this direction. In any case antipyrin here diverges considerably from acetanilide, the power of which in large doses to increase markedly the elimination of nitrogenous wastes has been clearly established.

**Local Effects.**—Externally, antipyrin has analgesic, vasoconstrictor, and antiseptic properties. It is mildly irritating when applied to mucous membranes, and if injected subcutaneously may induce necrosis of tissues and abscess formation. The analgesic and vasoconstrictor (hemostatic) effects are best obtained with 30 or 40 per cent. solutions (Wood). According to Saint-Hilaire, complete anesthesia of mucous membranes may be obtained with antipyrin in 30 per cent. strength. As an antiseptic the drug is capable, in 10 per cent. solution, of inhibiting the growth of certain pathogenic bacteria. According to Roux and Rodet, the *B. coli communis* is distinctly antagonized by it in 4 per cent. strength. Putrefactive processes are completely arrested by even weaker solutions. Weak solu-

tions of antipyrin also interfere with peptic and diastatic enzyme action.

#### **Absorption, Fat, and Elimination.**

—Antipyrin is rapidly absorbed from the gastrointestinal tract. In the dog it has been found to be in part oxidized in the system. In man it appears in the urine, according to Lawrow (1901), in the form of a double glycuronic acid, in which antipyrin itself is probably held in the form of an oxyantipyrin. Its chief route of elimination is by the kidneys, but it has also been detected in the saliva, the sweat, and the milk of nursing women. It begins to appear in the urine in three-quarters to one hour after ingestion, according to Perret and Givre; in five to twenty-five minutes, according to Pouchet. The elimination is not complete until after about thirty-six hours in adults, but is claimed to occur more rapidly in children.

Given in large doses,—in 2 capsules each containing 15 grains (1 Gm.), at intervals of two hours,—antipyrin may be detected in the milk, according to Fieux, in from five to eight hours after its ingestion, while from nineteen to twenty-three hours afterward none can be found; hence, its elimination lasts eighteen hours at the maximum. It passes into the milk only in a very low proportion—very much less than 50 mg. ( $\frac{1}{2}$  grain) in 1000 Gm. (1 quart) of milk. It is only under exceptional conditions—*e.g.*, when 60 grains (4 Gm.) are administered in sixteen hours—that it may reach this proportion. It does not influence in any way the quality of the milk. The secretion remains very abundant, provided the woman continues to nurse. From the absence of general symptoms and from examinations of the weight, the infinitesimal quantity absorbed by the nursing does not seem to have any unfavorable action.

Antipyrin appears in the urine, according to Lamanski and Main, forty minutes after being taken by the

mouth and thirty minutes after its introduction into the rectum.

Any of the substances producing coloration when added to aqueous solutions of antipyrin may be employed in testing the urine for it. Ferric chloride, however, is most generally employed for the purpose, revealing, by the red color produced, the presence of the drug in dilutions as high as 1:100,000.

**Untoward Effects.** — Under this heading will be considered those accidents which follow the use of antipyrin in therapeutic doses in a certain percentage of cases. It has repeatedly proven poisonous unexpectedly in persons accustomed to its use, even in small doses. Blebs about the mouth and gums have been observed. The penis and scrotum may also show a vesicular eruption which sometimes form scabs, or become cyanotic. It may cause twitchings.

Case of bullous eruption in the buccal cavity due to the ingestion of antipyrin. The writers call attention to the possibility of such eruptions being limited exclusively to this region. Nicolas and Moutot (*Ann. de Dermat. et de Syph.*, No. 11, 1911).

After taking 1 dose of 0.75 Gm. (12 grains) of antipyrin salicylate a colored man of 40, burning and edema was complained of to such an extent that it seemed that a caustic had been taken by mistake. Unaware that the drug caused the trouble, he took another dose. By the next day the lips and mouth looked as if lined with yellow cotton, and in two days the tissue affected was cast off, the cheeks, lips, gums and pharynx being thus denuded, and the whole course of the esophagus smarted and there was also pain in the epigastrium, whenever the man took any water or milk, the only things allowed. The ulceration was apyretic and healed in the course of two weeks without leav-

ing a trace. Two years before the man had had a similar experience, also after a single dose of antipyrin salicylate, but the connection with the drug was not suspected at the time. Idiosyncrasy could alone explain such results. De Bellard (Gaz. Med. de Caracas, Oct. 15, 1918).

A *skin eruption* is one of the most frequent of these unpleasant results and is, in fact, oftener seen after antipyrin than after either acetanilide or acetphenetidin. It is generally erythematous, and, according to H. C. Wood, "in its most typical form it consists of small, reddish, irregularly circular spots, resembling somewhat those of measles, and arranged in patches separated by sound skin." Urticarial and even bullous and eczematous types of eruption have also been recorded. *Edema*, particularly of the face or extremities, may accompany the eruption, which is also sometimes attended with fever and circulatory disorder. Pigmentation may follow, especially if the eruption has been produced repeatedly.

Of 488 cases of antipyrin poisoning reported by 299 observers in the literature from 1884 to 1907, 10, or about 2 per cent., are reported to have resulted fatally. In a number of instances a single dose of 5 grains (0.32 Gm.) or less has produced alarming symptoms, while a dose of 10 or 15 grains (0.65 to 1 Gm.) has produced serious collapse. Kebler, Morgan, and Rupp (U. S. Dept. of Agricul., Bureau of Chemistry, Bull. No. 126, July 3, 1909).

In a number of instances an antipyrin skin eruption has been associated with evidences of *anaphylaxis*.

Case in which the patient began taking antipyrin for migraine at the age of 24. After taking it 9 years, she showed symptoms of diabetes. Antipyrin then caused a rash which

reappeared after each dose—an erythema and vesicles about the lips. Yet she continued its use until the age of 42, when it was discontinued, after taking it 9 years without disturbance and 9 years more despite the disturbance. After 7 years without antipyrin, when admitted for diabetes, she received a dose of 0.5 Gm. (7½ grains). The rash recurred as before with the signs of anaphylaxis—fall of blood-pressure, marked leucopenia, and disturbances of blood coagulation. Other drugs, even pyramidon, so closely related to antipyrin, caused no disturbance. A dose of antipyrin of 2 cg. (⅓ grain) caused the reaction in 50 minutes, while with a dose of 1 cg. (⅙ grain) the result was negative. These small doses were then used to desensitize, and after some weeks even a massive dose failed to cause the rash. Widal and Pasteur Vallery-Radot (Gaz. des hôp., Feb. 7, 1920).

Case in which the drug had been taken only 2 or 3 times, and the anaphylaxis seemed to merge with the effects of certain foods. The patient was desensitized to antipyrin by repeated small doses, but this did not last long. A small dose of the drug 1 hour before the full dose always proved effective, however. The most intense effect on the leucocyte count occurred almost instantly. Labbé and Haguenau (Bull. Soc. méd. des hôp., July 29, 1921).

The *mucous membranes* in many instances show similar evidences of irritation or active vascular disturbance. Swelling of the buccal, nasal, and laryngeal mucosæ may occur, and catarrhal inflammation of the conjunctivæ has also been recorded. The respiratory mucous membranes may become so greatly engorged as to render breathing difficult.

*Nausea* and *vomiting* occasionally result where there is excessive gastric irritability. Burning sensations in the epigastrium and *diarrhea* may be produced even by moderate doses.

*Sweating* as an accompaniment of the action of full doses of the drug has already been referred to. In some cases, especially the tuberculous, it may be so pronounced as to become a source of great discomfort.

*Shivering* occurs where a marked fall of temperature has been produced by the drug, and is evidence of an attempt on the part of the heat-regulating centers, as the effect of the drug upon them is waning, to increase heat production through stimulation of oxidative processes in the muscles. This is, in reality, an effect for which the antipyrin is only indirectly responsible.

*Cyanosis* occurs less frequently after antipyrin than after acetanilide. This is doubtless owing to the fact that the former is much less active as a producer of methemoglobin than the latter. When cyanosis does occur, there is frequently dyspnea and cardiac acceleration. After large amounts of these drugs, cyanosis may result from circulatory depression, without any changes in the blood having necessarily occurred.

*Collapse*, like cyanosis, is less to be feared after antipyrin than after acetanilide, but it is said to occur more frequently with the former than with acetphenetidin. Though witnessed regularly in acute poisoning by massive doses of antipyrin, it has also frequently occurred under moderate doses of the drug, especially, though not exclusively, when used for the purpose of reducing fever. Sudden drops in the temperature are said particularly to invite the occurrence of collapse. The symptoms, of which the most important is cardiac weakness, may be but mild and transitory. In other cases, however,—more prop-

erly to be classed as acute antipyrin poisoning,—progressive circulatory enfeeblement may take place and death ensue. The cause of collapse under moderate doses may refer to some special circulatory weakness—temporary, as in acute infections, or permanent—or to idiosyncrasy, but collapse has also been ascribed directly to the sudden fall of temperature sometimes occurring, on the ground that heat is a stimulant, and that its absence or reduction is, therefore, conducive to depression. Menstruating women are said to be especially liable to collapse (Sollmann).

*Ischuria, albuminuria, and hematuria* are among the more rarely encountered untoward effects of antipyrin. The relative frequency of their occurrence seems to correspond to the order in which they are here given. Renal disturbances already present may figure as a predisposing factor.

Case of a woman of 29 who, twenty minutes after taking her usual remedy for headache, a 7½-grain (0.5 Gm.) cachet of antipyrin, began to sneeze violently and persistently. Lachrymation, running at the nose, and dryness of the throat were noted, followed by dyspnea and marked precordial distress. The face became suffused, the lower extremities began to itch, and an erythema appeared, extending upward from the limbs, and eventually becoming general, though the face was spared. The respiration resembled the Cheyne-Stokes type, and the pulse was 120, regular. The symptoms disappeared in a few hours after ingestion of hot tea and a hypodermic injection of caffeine, which induced copious diuresis. The itching was relieved with a mentholated paste and starch powder. The case was interesting in that there was shown a sudden intolerance to a dose of the drug habitually taken with impunity. The

intolerance was probably due to impaired renal function, as the patient had noticed on the preceding days that less urine was being passed than usual. Devoir (Bull. de la Soc. Méd. de l'Yonne, xlvii, 1906, p. ix).

Symptoms resembling those of cinchonism, especially *vertigo* and *tinnitus aurium*, are, in rare instances, produced.

Temporary *loss of vision* has been recorded several times.

Case of man 33 years old who had been in the habit of taking coal-tar analgesics for several years. Upon taking 130 grains (8.5 Gm.) of antipyrin within a period of forty-eight hours, vision became greatly impaired and two days after was entirely gone. Later it gradually returned. Hlotz (Arch. of Ophthal., No. 35, 1906).

A paradoxical *rise in temperature* has been mentioned by Lépine as occasionally following the use of antipyrin.

### ACUTE POISONING.

Of the symptoms witnessed when antipyrin is taken in poisonous amount, either in a single large or in repeated smaller doses, lassitude and cyanosis are among the first to appear. Typically the bluish hue is seen first in the face and hands, spreading later to other surfaces. There may be vomiting and abdominal pain. The pulse, at first, perhaps, accelerated, soon shows signs of weakening, and the extremities become cold. Drowsiness appears, the skin may become partially anesthetic, and consciousness is soon after lost. This may be preceded or accompanied by a stage of nervous excitement involving the lower brain-centers and spinal cord, manifested in exaggerated reflex irritability, tremors, or actual epileptiform convulsions. When this disturbance

subsides a pronounced fall in temperature and progressive collapse occur. The pulse becomes infrequent and feeble, the respiration is slow and stertorous—sometimes of Cheyne-Stokes rhythm—and the pupils are dilated and no longer react to light. Death may occur either from respiratory or circulatory failure. In cases that do not end fatally, itching of the skin and an erythematous rash not uncommonly appear during the period of recovery.

The lethal dose of antipyrin cannot be definitely stated, owing to the great variation in its effects in different individuals. In a case of Barr's (cited by Wood), 35 grains (2.25 Gm.) given to a puerperal woman, followed in three hours by half this amount, caused death. Forty-five grains (3 Gm.) had a fatal effect in a patient with cardiac weakness (Butler). In the average case 30 grains (2 Gm.) are required to induce dangerous symptoms, though in a few instances serious poisoning has been caused by doses of 10 grains (0.65 Gm.) or less.

Of 192 physicians questioned on the subject of antipyrin poisoning, 89, or 46.3 per cent., stated that they had observed toxic effects from this drug (as compared with 76 per cent. of 288 physicians having seen instances of acetanilide poisoning, and 21.5 per cent. of 306 physicians having seen instances of acetphenetidin poisoning). These 89 observers reported 105 cases of poisoning by antipyrin, including 5 deaths, *i.e.*, 4.7 per cent. The character of the fatal cases and the doses used were as follows:—

Pneumonia, 10 grains (0.65 Gm.) every two or three hours. Death on third day.

Fever (child), 20 grains (1.3 Gm.). Death in two hours.

Acute rheumatism, antipyrin dis-

pensed instead of "aspirin," quantity not stated. Patient died suddenly.

Headache, 10 grains (0.65 Gm.) followed by 15 grains (1 Gm.) in an hour.

Neuralgia, 5 grains (0.32 Gm.) every three to four hours; 1 dram (4 Gm.) taken in two days.

Kebler, Morgan, and Rupp (U. S. Dept. of Agricul., Bureau of Chemistry, Bull. No. 136, July 3, 1909).

**TREATMENT OF ACUTE POISONING.**—The patient should be placed in the recumbent posture and the clothes loosened. The stomach may be washed out, or an emetic administered, if it seems likely that some of the drug has not yet been absorbed; in cases with marked circulatory depression, however, the advisability of this measure is doubtful. The chief danger to be apprehended in this condition being circulatory failure, stimulants such as **caffeine** or **hot, strong coffee**, **digitalis** or **digitalin**, **strychnine**, **atropine**, **camphor**, and **aromatic spirits of ammonia** or **ammonium carbonate** are indicated. Dyspnea, if severe, may be relieved by **oxygen inhalations**. **Saline solution** by enteroclysis or hypodermoclysis may be availed of. The application of **external heat**, to compensate for the excessive amount lost, is a valuable measure. **Artificial respiration** is helpful in desperate cases.

### CHRONIC POISONING.

Reported instances of chronic disturbances caused by the continual ingestion of antipyrin, similar to those induced by acetanilide, are exceedingly few—so much so that antipyrin would appear to be a much safer drug in this respect than acetanilide and even acetphenetidin. Skin affections; **edema**, especially facial; digestive disturbances, mental hyperexcitability, and

pronounced tremor are the symptoms which have been most frequently witnessed after the prolonged use of antipyrin. Dauernst observed a case in which the nervous symptoms produced by the drug resembled those of disseminated sclerosis.

In the replies of 400 physicians to a set of questions, 112 instances of acetanilide habit were reported, 7 of antipyrin habit, and 17 of acetphenetidin habit. Ill effects were observed in 85 of the acetanilide cases, 2 of the antipyrin cases, and 7 of the acetphenetidin cases. Kebler, Morgan, and Rupp (U. S. Dept. of Agricul., Bureau of Chemistry, Bull. No. 136, July 3, 1909).

**TREATMENT OF CHRONIC POISONING.**—For information concerning the management of these cases the reader is referred to the corresponding section under Acetanilide.

**THERAPEUTICS.**—As **Antipyretic**.—In febrile cases, provided the temperature be very high, the use of coal-tar antipyretics, including antipyrin, is still sometimes recommended, though in recent years the tendency has been to discard these drugs whenever other means to a similar end, especially hydrotherapeutic measures, can be employed. It is only in cases of **hyperpyrexia** (temperature above 105.5° F.) that a drug such as antipyrin may be said to be indicated.

However favorable the high temperature in these cases may be for the destruction of noxæ, a great waste of the nitrogenous body constituents takes place through accelerated catabolism, and this state of affairs leads rapidly to emaciation, diminished alkalinity of the blood, and degeneration of important organs (Sollmann). It becomes necessary,



therefore, to apply simultaneously all effective methods of reducing the temperature at our disposal, including the coal-tar drugs, even though, in cases where the fever is more moderate, these drugs have no advantage over cold baths, except in sparing the patient the inconvenience and exertion which the latter entail. In cases with known or suspected cardiac or renal weakness, however, special caution in dosage is required, or, preferably, total abstention from the use of the drug. In typhoid fever especially are untoward results to be feared and guarded against. Since febrile cases in general are well known to be more susceptible to the unfavorable or dangerous effects of the coal-tar drugs than the afebrile, it is well to administer the antipyrin in small, frequently repeated doses rather than massive single doses. Thus,  $7\frac{1}{2}$  grains (0.5 Gm.) may be given at first, and repeated later if the action is inadequate or when it begins to wear off.

The effect of antipyrin on the temperature begins in about half an hour after its ingestion, and continues for a variable number of hours (from two to ten, according to Wood). Pronounced diaphoresis frequently accompanies the action of antipyrin—distinctly greater, on an average, than that observed after acetanilide or acetphenetidin.

In addition to these effects the drug may to a certain extent overcome restlessness and delirium—a fact which formerly caused antipyrin to be used considerably in the febrile affections of children (**pneumonia, typhoid fever, scarlatina**, etc.), irrespective of hyperpyrexia.

[So many deaths occurred when antipyrin was used as an antipyretic that it is

preferable never to use it in febrile infections. Its antipyretic action even at best is but an artificial one, since it is only the surface temperature that is reduced, while the central temperature is raised. This applies also to chronic febrile infections referred to below. C. E. DE M. S.]

In the hectic febrile movements of **pulmonary tuberculosis** antipyrin has been tried, sometimes with asserted satisfactory results. The diaphoretic action is, however, a marked disadvantage. In the long run, the drug proves too depressing, and cannot be recommended in these cases, all the more since a certain degree of tolerance to it may be established upon repeated use, necessitating an increase in dosage for the securing of adequate effects.

In **intermittent fever**, antipyrin has also been used; it exerts no specific action on the causative plasmodium, and is, therefore, in general, immeasurably inferior to quinine. In chronic forms of malaria, however, it has sometimes proven beneficial where quinine failed to act (Antony). In severe malarial cases where it is desired to inject quinine hypodermically, antipyrin has been given in combination with this drug, according to Laveran's formula (quinine hydrochloride, 3; antipyrin, 2; distilled water, 6); the antipyrin increases the solubility of the quinine salt. Santeson found this plan satisfactory.

**As Analgesic.**—Antipyrin is now of far greater importance as an analgesic than as an antipyretic. Its efficacy in pains of the neuralgic type has brought it into deserved prominence as an advantageous substitute for morphine in these cases. In certain conditions its effect is actually superior to that of opiates. In pain arising from inflammatory dis-

orders, however, its action does not replace that of opium.

In **migraine** and other forms of **neuralgia**, amounts ranging from 5 to 15 grains (0.32 to 1 Gm.), given in successive doses of 5 grains (0.32 Gm.) each, at one-half to one hour intervals, will in most instances give relief. **Sciatic** pains also frequently yield to antipyrin, though with less uniformity than other varieties of neuralgia.

In the "lightning pains" and "gastric crises" of **tabes** antipyrin has been prescribed with variable results. Doses so large as to be more or less unsafe are generally required to produce an impression on these pains.

In **herpes zoster** ("shingles") the drug is often effective.

Antipyrin by rectal injection is recommended by the writer. Montenius has used it in the form of a small rectal injection in **infantile convulsions** and vomiting in doses of from 0.25 to 0.5 Gm. (4 to 8 grains) dissolved in 15 c.c. ( $\frac{1}{2}$  ounce) of water. Guyon and Guiard found that given in this way with the addition of a small dose of opium, antipyrin acts as a marked sedative in disorders of the **bladder**, especially in **prostatic disorders**. Mastboom employs antipyrin in the treatment of pelvic **neuralgias**, **dysmenorrhea**, and **coccygodynia**, according to the following formula which he has employed in a large number of these commonplace disorders.

**R** Cocaine hydro-  
chloride .... 0.10 Gm. ( $\frac{1}{2}$  gr.).  
Antipyrin .... 10 Gm. ( $2\frac{1}{2}$  dr.).  
Distilled water. 30 Gm. (1 oz.).

Of this solution 1 teaspoonful is to be administered in the form of an enema. A. Guérin (Jour. de Méd. de Bordeaux; Med. Rec., Jan. 25, 1913).

The value of antipyrin in **chronic rheumatic** or **gouty** pains was empha-

sized by Germain Sée. In **acute rheumatism** the drug was also lauded by the same author as being superior to salicylates in *afebrile* cases. According to Manquat, antipyrin is preferable to salicylates in cases where there are cardiac complications, especially where the organ is in a state of "erethism," as it is less of a depressant to the heart than salicylates (exception is to be made, however, of cases having an idiosyncrasy to antipyrin). He quotes Clément, moreover, as having found antipyrin to hasten the resolution of serous involvements in this affection.

In **influenza**, especially where attended with pains in the back and headache, antipyrin has proven itself a valuable remedy. The greater the asthenia in any given case, however, the more caution should be exercised in its use. Acetphenetidin, the mildest of the coal-tar analgesics in common use, is sometimes recommended in preference to antipyrin.

In **pseudoangina pectoris** antipyrin has been lauded as an analgesic. In true angina pectoris, however, granting that antipyrin is a constrictor of the central blood-vessels, the use of the drug would seem to be irrational, though Sée reported having arrested anginal attacks in 4 cases by means of injections of antipyrin and inhalations of pyridine (Manquat).

**As Antispasmodic and General Sedative.**—In whooping-cough antipyrin is used as a sedative with marked benefit in many cases. It probably exerts no advantageous effect on the course of the disease in general, though le Goff has claimed that the duration of the affection is shortened. Its chief service is that of lessening the frequency and sever-

ity of the paroxysms of coughing, seemingly by diminishing the irritability of the superior laryngeal nerve or its receptive center. Dubousquet-Laborderie used antipyrin in 300 cases, with 9 deaths; he gave it in daily doses of 0.2 to 0.3 Gm. (3 to 5 grains) at first, later increased to 1.5 Gm. (23 grains) or more. In very young children it is best given immediately after the paroxysms; in older children, with the meals.

Antipyrin found to be the most serviceable of all drugs in an epidemic of **whooping-cough**. It seldom failed after two or three doses to stop the vomiting after the coughing spells, even in cases where it did not appear to influence the paroxysms themselves. In most instances the frequency of the latter would diminish to one-half or less. The dose usually found efficient was 1 to 3 grains (0.065 to 0.2 Gm.) four to six times daily. By doubling the dose at bedtime, a comparatively quiet night's rest was often obtained. H. N. Fletcher (Practitioner, April, 1907).

Report of cases of **pertussis** in which 15 drops (0.9 c.c.) of a 2 per cent. solution of antipyrin were injected into the larynx, with marked success, by means of a special pipette devised by Yankauer. Fendler (Amer. Jour. of Obstet., June, 1908).

Quinine and *antipyrin* can be depended on to abort or attenuate **pertussis**, but, as usually given, the dislike of the child to take the medicine leads to inadequate dosage or to its total neglect. This can be obviated by injecting a solution of the drug into the rectum. The writer has 1 Gm. (15 grains) dissolved in 25 Gm. (6 drams) warm water and injected three times a day, for a child over 12, with smaller doses for children younger. No ill effects have ever been noticed on the heart, while, when the injections are commenced early, the disease is frequently aborted. It does not depress the

appetite given in this way, and the therapeutic effect seems to be constant and reliable. Senftleben (Deut. med. Woch., Jan. 14, 1909).

In **chorea** antipyrin is highly recommended by some observers, though in the hands of others it has not yielded any particularly striking results. According to Scribner, the drug is effective in reducing the spasmodic movements and in relieving the muscular and joint pains. Progressive increase in dosage is often necessary in order to keep up the primary beneficial results. It is recommended, however, to give the drug in small, frequently repeated doses, rather than fewer, massive doses, in order that, upon the appearance of untoward effects (cyanosis especially), the sudden and tardy advent of which is one of the unpleasant features of the action of this drug, stoppage of the remedy may lead to a more prompt arrest of its action. For a child of 5 years the proper initial dose would be 2 or 3 grains (0.13 to 0.2 Gm.) every three or four hours. The drug should not be administered too long. Small doses of digitalis may advantageously be combined with it for greater safety (Scribner).

In some cases of **hay fever** antipyrin in full doses has been found useful, though it should not be continued for any length of time.

In **exophthalmic goiter** antipyrin has occasionally proven useful. Cazal employed it to reduce nervousness through sedation of the centers. Hinchelwood reported a case in which it removed Stellwag's symptom (retraction of the upper lid), though Graefe's symptom persisted.

Antipyrin has been employed with indifferent success as a nerve seda-

tive in certain other affections, including epilepsy, bronchial asthma, and seasickness.

In children antipyrin has proven useful as a general sedative in many conditions associated with evidences of excessive irritability of sensory nervous structures. In small doses it seems to be almost uniformly well borne in childhood, and its freedom from hemolytic action and from the tendency which acetanilide and acetphenetidin possess to produce cyanosis is an advantage.

Antipyrin found useful in conditions of nervous irritability, pain, sleeplessness, etc., associated with **teething**. **Nervous instability** leading to vomiting, diarrhea, cough, or even eczema at the eruption of every new tooth or set of teeth is sometimes removed, and the symptoms checked, by antipyrin. This includes those cases of rickets in which **dentition** is associated with nervous symptoms, though, of course, antirachitic treatment is indicated in addition. Dose used, 1 to 2 grains (0.65 to 0.13 Gm.) two or three times daily. The drug proved strikingly effective in 3 children with "night terrors." The true cause, *e.g.*, depressed general health, digestive disorder, rickets, congenital syphilis, or adenoids, must, however, always be sought and removed in these cases. H. N. Fletcher (Practitioner, April, 1907).

In **dysmenorrhea** its use was recommended by E. C. Rothrock and E. E. Montgomery.

For relieving the so-called "**after-pains**" succeeding childbirth antipyrin has been found useful. It has also been used with some benefit for the purpose of quieting a tendency to the development of pains before the full term has been reached.

During **lactation** antipyrin may be given to control or suppress the mammary function.

In **diabetes mellitus** antipyrin brings about a prompt, more or less marked, but merely temporary diminution in the degree of glycosuria, as well as of other symptoms. According to Manquat, cases in which the elimination of sugar does not exceed 80 to 100 Gm. (2½ to 3 ounces) to the liter of urine can be entirely relieved for a time by a combination of antipyrin with suitable diet; where the glycosuria is more pronounced, improvement may nevertheless be obtained; but in emaciated patients, with glycosuria exceeding 150 Gm. (5 ounces), no results whatever are to be expected. Even in favorable cases, continued benefit from antipyrin can only be obtained by intermitting the administration of the drug from time to time, *e.g.*, giving it for eight or ten days, then stopping it for a week. Digestive disturbances and albuminuria may result upon continued use of the drug. The present tendency is to restrict the use of antipyrin to cases showing particular nervous phenomena, such as undue excitability, restlessness, etc.

The manner in which the coal-tar drugs act in diabetes is not known. According to some, they act as nerve sedatives, controlling the excessive glycogenesis resulting from nervous overactivity.

In **polyuria** of medullary origin, antipyrin is known to be effective. In that of interstitial nephritis, however, it does no good and, in fact, is contraindicated (Huchard).

**Local Uses.** — Locally, antipyrin may be employed for its analgesic, antiseptic, and styptic effects. St. Hilaire and Coupard have used it in conditions attended with **pharyngeal** and **laryngeal** irritation, and have demonstrated its useful local anes-

thetic properties. They recommend a solution of 1 part of the drug in  $2\frac{1}{2}$  parts of distilled water, employed as a spray. According to the former observer, the complete insensibility produced by this strong solution persists for one to two hours.

The writer lays stress on the value of antipyrin as a **local anesthetic** now often employed as a styptic in hemorrhage. Its astringent action renders it suitable also in painful inflammations, such as **stomatitis**, **gingivitis**, etc. While its action is not as strong as that of cocaine, relief is more lasting and effective, because the process of inflammation is abated. Even in **ulcerative carcinoma** of the tongue, antipyrin is very effective in alleviating the **glossitis** complicating these ulcerations. For these local applications by painting, a simple aqueous solution of 1:10 is employed. For mouth-washes or gargles a 1:50 solution is used. The disagreeable taste of antipyrin can be considerably improved by the addition of glycerin. A. F. Plicque (*L'Odontologie; Dental Cosmos*, Jan., 1913).

Under ordinary circumstances, however, a 2 to 4 per cent. spray is sufficient to afford relief in **acute coryza** or pharyngeal irritation. Antipyrin brought in contact with mucous membranes causes considerable smarting and burning, especially if used in 4 per cent. or stronger solutions; it is, therefore, advisable always to precede its use by the application of cocaine.

In **tonsillitis** antipyrin may be used in the form of a gargle. Some care is, of course, necessary as to dosage, and the patient should be instructed not to swallow the solution after gargling.

In **cystitis** with ammoniacal urine Cazeneuve found antipyrin in 4 per cent. solution serviceable. The pain was diminished and the character of the urine improved.

**Pruritus** is sometimes relieved by antipyrin.

As a local anesthetic in operative procedures involving mucous membranes antipyrin has been used to some extent, but in comparison with the numerous good local anesthetics more recently introduced it presents no advantage.

Clinical experience with antipyrin as a local anesthetic. Employed in 50 per cent. solution as a local application to the mucous membrane of the nose, it brought about a deep anesthesia. However, it was so slow in its action that even when used with adrenalin several applications at intervals of two to three minutes had to be made before insensibility of the membrane resulted.

The writer also reports the use of antipyrin by injection, preceded by the application of quinine and urea hydrochloride and adrenalin to the mucous membrane, for the resection of the turbinate bones, having employed it successfully 23 times without ill effects. A. Ephriam (*Kentucky Med. Jour.*, Nov. 1, 1911).

Hypodermic or intramuscular injections of a 25 to 50 per cent. antipyrin solution have been given in order to secure the analgesic effect directly at the seat of pain in such conditions as **sciatica**, **supraorbital neuralgia**, etc.

Bergquist employed this measure, followed by massage at the point of injection, in 130 cases of **lumbago**, and reported 122 as having been cured. The injections themselves, however, caused very sharp pain lasting half a minute. They have also been known to produce local necrosis and abscess formation (Ricochon and Verneuil).

In the presence of neuritis such injections are believed to be especially injurious.

In **local hemorrhages** antipyrin is valuable as a styptic. It is believed to act by constricting the vessels and inducing retraction of the tissues. The antiseptic property of the drug is also useful under these circumstances, antagonizing the development of bacteria in the clot. In **epistaxis** antipyrin may be applied to the bleeding point in a 10 to 50 per cent. solution by means of a tampon. The first-named strength of solution is generally sufficient for all ordinary purposes. The employment of a sterile 5 per cent. solution as a spray, on a compress, or as an injection has been recommended. In addition to epistaxis, the drug has been used with success in **dental, tonsillar, and uterine hemorrhages.**

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

**ANUS, DISEASES OF.** See  
RECTUM AND ANUS, DISEASES OF.

**APHASIA.—SYNONYMS.**—  
Aphrasia; alalia.

**DEFINITION.**—Aphasia is a partial or total loss of the power of expressing one's self in speech or of understanding speech, which is dependent upon cerebral disorder.

**VARIETIES.**—Two chief divisions of the affection: motor, or emissive or projective, aphasia, and sensory, or receptive or subjective, aphasia are recognized. Each variety includes at least two elementary forms: aphemia and agraphia, as motor subdivisions, and visual aphasia, or word-blindness (alexia), and auditory aphasia, or word-deafness, as subvarieties of sensory aphasia.

The motor aphasia may be complete (aphemia) or there may be only some partial defect in the emissive mechanism of speech (dyslexia, paralexia, articulative ataxia, paraphasia, paralalia). The agraphia may likewise be complete (agraphia) or partial (paragraphia, dysgraphia). Pantomimic speech, so called,—which is an emissive form of speech in gestures, signs, etc.,—may be affected totally (amimia) or partially (paramimia) also. The more elaborate subdivisions of sensory aphasia are based upon qualitative rather than quantitative impairment. In the older literature all forms of sensory aphasia were referred to collectively under the term "amnesic aphasia," which included loss of the pictorial memory of letters and words and of the sounds of letters, words, and music. It included, also, loss of the power of understanding the meaning of figures, written music, and other symbols.

In the more recent literature of the subject the term "amnesic aphasia" has been rather arbitrarily restricted to a loss of the naming rather than the ideational functions of speech-memory. Loss of the ideational faculty is expressed by the term "apraxia" (mind- or soul- blindness). Both sensory and motor aphasia may be divided, as regards the anatomical basis, into the cortical and subcortical varieties. The terms "conceptional" and "conductive" are practically of identical significance with the terms "cortical" and "subcortical."

The writer lays stress upon the necessity for 8 forms of tests, tests for spontaneous speech, for repeated words, reading aloud, spontaneous writing, writing from a copy and writing from dictation, study of comprehension of spoken words, and

study of comprehension of printed words.

In apraxia the simple reflex and expressive movements must be studied as well as the descriptive and other movements, as he enumerates in detail. Laignel-Lavastine (*Bull. méd.*, Mar. 20, 1920).

In a study of the difficulty in finding the proper word in aphasia the writer found that the difficulty is much greater for names of unseen objects than for the visible, and that this must be borne in mind, in addition to other features while in training during convalescence when total aphasia exists. F. Lotmar (*Schweizer Archiv f. Neurol. u. Psych.*, Apr., 1920).

**SYMPTOMS. — Motor Aphasia (Aphemia).**—In motor aphasia the voluntary act which must be carried out to give expression to thought by the phonetic co-ordination of the muscles of the larynx, tongue, soft palate, and lips is not performed. The patient is seldom unable to produce sound, but he can no longer produce an articulate sound. Although he understands what is said and can think, he is unable to give expression to his thought; it may be possible for him to pronounce letters or even meaningless words,—he may even retain some words,—but these are usually interjections of some kind. In some cases, nouns only or verbs only are forgotten. One language may be forgotten and another remembered. This variety of aphasia is usually encountered in persons who are affected with right hemiplegia. In some, however, who are left-handed, there may be left hemiplegia. In some cases, although speech is impossible, the patient can articulate in singing, especially if certain well-known airs are sung, the words in that case having become intimately connected with the notes.

Mental retardation in children may be due to congenital word-blindness and word-deafness. Disabilities in the zone of language may induce affective states leading to serious character and behavior difficulties. Teachers should distinguish these disabilities from defective intelligence, that remedial measures may be applied. E. B. McCready (*South. Med. Jour.*, Sept., 1925).

**Agraphia.**—Agraphia consists in the loss of the memory of the necessary movements to write. In an uncomplicated case the patient is able to speak, hear, or read as usual, but when he tries to write he finds that he can no longer do so, though he is capable of copying letters or designs placed before him. Pure agraphia is uncommon. It is usually associated with some aphemia.

Agraphia can only occur in those persons whose education is sufficient to enable them to write automatically.

**Amimia.**—Sign-language, as practised by deaf-mutes in gestures and pantomimic speech generally, may be affected by a cerebral lesion. Loss of pantomimic speech is often coexistent with aphemia or agraphia or both. It is rarely or never found alone, although it is quite possible to conceive of its separate existence in one in whom this faculty had been especially cultivated (Mills).

**Sensory Aphasia.—Auditory Aphasia.**—This variety is more rarely met with than motor aphasia. Both the reception and production of audible speech are deficient, the leading symptoms being, on the receptive side, word-deafness and, on the productive side, word-amnesia and articulative amnesia. Speech and separate words are distinctly heard by the subject, but no meaning is attached to them. Sounds, however,—such as that of an engine-whistle, an alarm-clock, the hour,—are

heard and recognized. Right hemiplegia and a certain amount of word-blindness are frequently present. Certain cases of auditory aphasia hear as if spoken to in a foreign tongue, but they cannot understand what is said, although they endeavor to do so. Other patients understand neither what is said to them nor what they themselves say, but can repeat words after another. They repeat like parrots (echolalia) what is said; but if the center of articulate voice is still partially connected with the sensory centers of audition and the latter are normal, the repetition of the word may suddenly give rise, in their mind, to the idea conveyed by the word.

Instead of articulate speech the phenomena may show themselves in connection with music or numbers. In subcortical word-deafness the patient hears, but does not understand. He can, however, repeat at once whatever he hears, and write it down. While writing or speaking he may understand the words used, but not after the mechanical act is accomplished.

Macleod Yearsley has pointed out that this condition is especially important in connection with the examination of school children. Thus, a child aged 11 is very bright and healthy, except for her defect in hearing for spoken speech, and rather more intelligent than normal children of her age. When spoken to she makes an attempt to repeat the sound, but if she sees the lips she does as she is told, and answers as far as she can rationally. The functional tests, after her education has proceeded somewhat by the oral method of treatment, show practically normal results, and the tympanic membranes are healthy. Yet, she can be more easily taught by the oral method, though her response to questions heard is improving. It is difficult to explain such cases on any hypothesis save that of weakness of the auditory center.

*Word-blindness (Alexia).*—The patient sees written or printed letters and words and may be able to distinguish one from another, but they no longer have any meaning for him. Word-blindness is rarely total, however, a few words or letters being usually understood; nor is the disorder often found existing alone. In nearly every case there coexists either word-deafness or motor aphasia or some other complication of speech.

Word-blindness is often found in connection with right lateral hemianopsia, or concentric diminution of the field of vision. The patient can no longer read, but can write; as he cannot read what he has written, the letters and lines are sometimes uneven and resemble those written with the eyes shut. In the right hemianopsia found in this connection the written lines always begin on the left side of the page. The visual memory of numbers may be preserved or may also be lost (*cacitas numeralis*). Word-blindness can, therefore, be divided into two categories: In the one, the sense of the letter itself is lost (*cacitas literatis*); as a consequence, persons who generally read slowly, and spell out each word, suffer the total loss of the power of reading. In the other, the accompanying hemianopsia prevents the general physiognomy of a word being rapidly taken in by the patient (*cacitas verbalis*).

The writer reported in 1907 4 cases of congenital word-blindness occurring in the same family. Thomas, in 1905, called attention to the fact that congenital word-blindness might assume a family type, and that an hereditary origin was probable. The 4 cases of the writer support this contention, while the 2 now recorded still further confirm the hereditary tendency, since they occur in the second generation of this same family, and are



the children of the oldest daughter; hence, the nephew and niece of the cases previously reported. James Hinshelwood (*Brit. Med. Jour.*, Mar. 18, 1911).

**Subcortical Word-blindness.**—In subcortical alexia the patient can read or copy, but he does not understand what he does until the movement of his hand awakens in his mind the sense of word-hearing and of motor articulation through the muscular sense.

In pure verbal blindness the meaning of the words may be lost, but, by following with the eye the form of the letters, the patient finally may spell out the word.

**Apraxia.**—In apraxia (Kusssmaul) the patient no longer recognizes the use of objects which he sees; a fork to him conveys no meaning of its use. Apraxia may affect other senses besides that of sight,—as, for example, hearing, taste, smell, etc.,—the sound of a bell may no longer convey a meaning or the taste of a dish.

**DIAGNOSIS.**—In all cases of actual or suspected aphasia the patient should be examined as to his ability:

1. (a) To speak voluntarily; (b) to speak clearly and distinctly, pronouncing properly; (c) to repeat words dictated aloud.
2. (a) To write voluntarily letters, words, numerals, and sentences; (b) to write from dictation; (c) to copy; (d) to understand what he has written.
3. (a) To understand words and sentences spoken; (b) to understand or recognize vocal and instrumental music; (c) to understand the use of objects named.
4. (a) To read words, letters, numerals, and musical symbols if previously familiar with them; (b) to call objects by their names; (c) to recognize the use of objects exhibited; (d) to read and comprehend what is read.
5. (a) To name

and recognize the use of objects felt, tasted, or smelt.

**Word-deafness** must be distinguished from deafness. If the patient does not suffer from aphemia, it will be at once perceived, from his ability to hear simple meaningless sounds, that he is not simply deaf. When word-deafness exists in combination with aphemia and word-blindness (this latter complication is uncommon) the diagnosis must be made between true word-deafness and apparent deafness with dumbness in a non-hemiplegic, demented subject.

If, however, the symptoms have followed an apoplectic stroke with right hemiplegia, the affection is probably word-deafness due to a cortical lesion.

**Word-blindness**, if isolated, is easily recognized.

Katz reported 2 cases among public school children in both of which there was said to be alexia. Besides the real inability to read on account of congenital word-blindness, there was a pseudoalexia due to astigmatism and other congenital visual defects in a boy in whom the proper glasses corrected the alleged alexia. Visual defects which give an apparent alexia in children may be due to irregularities in the development of the eye as the result of hereditary syphilis.

**Aphasia, or Aphemia.**—Aphasia should be diagnosticated from (1) mutism due to melancholia; (2) mutism due to hysteria; (3) the silence observed in hemiplegic patients who speak with difficulty; (4) the silence observed in hemiplegic patients who are suffering from pseudobulbar paralysis of cerebral origin; (5) word-blindness associated with word-deafness. All these present individual characters which must be studied in connection with the general symptomatology of each affection.

Case of left-sided motor apraxia in a woman who had had an apoplectic

attack, resulting in paralysis of the left lower limb. The left side of the face was somewhat affected, but the left hand and fingers moved almost normally, exhibiting, however, 2 unusual phenomena, *viz.*, apraxia and Schuster's "forced grasping." The apraxia of the left hand was evidenced by inability to make a fist on command or to show with the left hand how one played the piano, although otherwise active motion of that hand was good. The forced grasping phenomenon consists of inability to open the hand when there is anything in its grasp, though there is ability to open it when it is empty. At autopsy an area of softening was found involving the right first frontal gyrus, paracentral gyrus, and right half of the corpus callosum. The last-mentioned lesion accounted for the apraxia. Pincas (Monat. f. Psych. u. Neur., lvi, 43, 1924).

**Agraphia** arising from a lesion of the center of writing should be distinguished from (1) the purely motor inability to write due to hemiplegia and (2) the agraphia due to a lesion of the visual center in patients of limited education and who copy visual images; (3) the agraphia due to a lesion of the auditory center, in which the patient writes only what is mentally heard by him, but cannot write from dictation.

The coexistence of word-blindness or of word-deafness with agraphia should suggest that the latter might be due to a lesion of the sensory centers (visual or auditory), especially if the patient did not previously write automatically, for agraphia due to a pure lesion can arise only in cases in which automatic writing has caused the development of a special graphic center.

**Infracortical Motor Aphasia.**—A pure motor aphasia without word-blindness or word-deafness is likely to be of infracortical origin. Cases, how-

ever, have been reported in which an infracortical lesion has caused aphasia, word-blindness, and word-deafness.

**ETIOLOGY.**—The various varieties of aphasia occur almost always as a manifestation of cerebral lesion. The most common factor is softening from hemorrhage, embolus, or thrombus; next in frequency are cerebral tumors and, especially, syphilitic lesions (Fournier); traumatisms, and meningoencephalitis.

Aphasia may temporarily occur in the course of many acute febrile infections—of the puerperal state, diabetes, nephritis, and gout—without any evidence of organic lesion. General writers have noted its occurrence in typhoid, especially in children and most frequently in boys; and in acute pneumonia, also, aphasia is met with apart from any other cerebral sign of cranial lesion. Aldrich has recorded a case of otherwise uncomplicated small-pox in a boy aged 7 years. He spoke no word for three months after the fall of temperature.

Among 100 aphasic inmates of the Western Pennsylvania Institution for Feeble-minded, Henninger found 35 were epileptics, 14 also paralytics; 20 were cases of cerebral paralysis, and 44 patients were idiots; 29 of the genetous type and 11 microcephalous, 2 hydrocephalic, 2 mongolian, and 1 cretin. Epileptic dementia from severe and frequent convulsions was credited as the cause of the aphasia in 6 of the epileptics, but in most of these cases Henninger considered both the aphasia and the epilepsy alike due to some developmental defect and advises a careful search for mechanical impediments to speech. If the patients do not then respond to treatment, an unfavorable prognosis should be given. In cases of cerebral paralysis, an attempt should be made to educate the uninjured hemisphere whenever there appears to be any possible chance of improvement.

**Agraphia in a case of frontal tumor.**

This case was of a somewhat unusual character, because of the presence of agraphia as a comparatively isolated symptom in the early stage of the disease, and, even when to this was

added difficulty in use of words and in obeying more complicated spoken commands, still the agraphia was the distinctive feature. Monakow asserts that "pure agraphia" occurs only as a hysterical phenomenon; its relatively isolated occurrence as a symptom without aphasia or apraxia is very rare. The writer also gives a *résumé* from literature of 8 cases of apraxia in 2 of which the left frontal lobe was involved; in the third case the lesion involved the white matter of the frontal convolutions. C. MacFie Campbell (Review of Neurol. and Psych., June, 1911).

About 80 per cent. of all cases of aphasia seen by the writers could be traced to the use of obstetric forceps during delivery. This is not surprising when one considers the condition of the bony tablets at birth and the amount of pressure frequently exerted upon them. Sometimes the inner tablet is split, a callus is formed upon its inner surface through the escape of osteoblastic cells, and thus a dent remains. Chapman, Morris and Simrell (N. Y. Med. Jour., Aug. 2, 1913).

Aphasia may present itself during enteric fever, small-pox, and puerperal fever. Transient aphasia—following epileptic or hysterical convulsions, migraine, or concussion of the brain—has been occasionally observed, and certain degrees of the affection may be temporarily present and even recurrent in states of profound anemia of the cerebrum and in alcoholism of the chronic type.

The hysterical mutism described by Charcot is, according to Courmont, nothing else than aphasia of transmission (aphemia) uncomplicated by agraphia, or verbal deafness or blindness. A mutism is met with in hysterical subjects which may be termed voluntary, is not due to aphasia, and should be differentiated from the hysterical mutism of Charcot.

A transient aphasia occurring in high blood-pressure and arteriosclerosis was

emphasized by Osler. The symptoms tend to repeat themselves in the attacks. There is inability to talk, consciousness of it, no paralysis, emotional disturbance, and, within a few hours, complete recovery; agraphia, hemianopsia and paresthesiæ may coexist.

Excluding syphilitic cases, the average age of the author's aphasia patients had reached the seventh decade of life. Cardiac, arterial, or renal changes were frequent. It may be assumed that there is commonly in these cases some degenerative change in the cortex or other tissues of the brain with deficient blood supply, the occurrence of aphasia marking a more definite pathological change in some part of the speech areas of the cortex. This complication increases the gravity of the prognosis and such cases frequently die of cerebral hemorrhage or softening.

Aphasia may supervene on pre-existing insanity or mental decay, no doubt due to vascular or degenerative changes, which might have led to the same result in the absence of the mental disorder. Again, aphasia may be the first symptom indicative of cerebral and mental decay. In such cases the question arises how far the mental disorder is intimately associated with the aphasic disturbance of speech or is due to widespread vascular and nutritive changes in the brain. The mental disorder does not necessarily amount to certifiable insanity, but may in varying degrees affect such mental processes as perception, memory, emotion, and volition, without much disorder of conduct. In all the writer's cases, except those of Broca's aphasia, there was some disorder of mind, though not always marked failure of intelligence. R. Percy Smith (Jour. of Mental Sci., Jan., 1918).

Two cases asserted to have been affected with aphasic dementia. The first had lost the power to speak, read or write, but could sing correctly all the words of a familiar song. The second spoke freely, with long sentences, but all his words were an unintelligible jargon. He understood

nothing of what he read. In every other field, he acted rationally. Civilized men do their thinking by means of language, and not by images, such as are sufficient for animals. When linguistic representation of objects is lacking because the organ of construction of verbal symbols is destroyed or has lost its function, thought is inhibited and the reasoning process reduced to the most elementary constructions. The aphasic subject is demented because he is aphasic, and not the opposite. He is capable only of immediate sensory reasoning which does not require language. L. Bianchi (*Ann. di nevrol.*, xxxviii, 143, 1921).

A boy of 18, after an attack of diphtheria, had hemiplegia and virtually complete aphasia through physical inability to evolve certain sounds, loss of kinesthetic memory and panic at the mistakes made. Recovery was obtained in 6 months by **systematic exercises** addressed to each of these phenomena, including visual memory. E. B. McCready (*Va. Med. Monthly*, Aug., 1921).

### **PATHOLOGY.—Motor Aphasia.**

—Pure aphasia of articulation was long ascribed solely to a lesion of the foot of the third left frontal convolution (Broca's convolution). If the lesion affected more than this region, it was held, other symptoms would be present. If the lesion occupied but a portion of the region, the aphasia might be partial only: for instance, nouns only would be missing.

In persons habitually left-handed a lesion of the third right frontal convolution may produce motor aphasia. In ambidextrous persons the aphasia is slighter and more transient.

The lesion may be either cortical or subcortical. As a rule, in the subcortical cases the defect is rarely complete.

Marie wrote in 1906 a series of very forcible articles denying any relation-

ship whatever between lesions of the third left frontal convolution (Broca's) and defects of motor speech. He localizes all speech functions in that region of the brain known as "Wernicke's zone," which includes the posterior part of the insula and of the lenticular nucleus and the posterior part of the first two temporal convolutions and part of the occipital lobe. He denies the existence, indeed, of motor aphasia, substituting the term *anarthria*.

Marie claims that Broca's convolution is not concerned in what is usually called "pure motor aphasia," but that the lesion

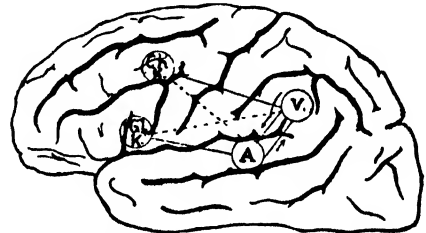


Diagram showing the approximate sites of the four word-centers and their commissures. (*Bastian.*)

is situated in a quadrilateral area bounded in front by a transverse line leading from the anterior end of the insula to the lateral ventricle, internally by the ventricle and the internal edge of the hemisphere, behind by a transverse line leading from the posterior end of the insula to the internal edge of the hemisphere. Marie is inclined to limit the localization still more to a "lenticular zone" situated between the convolutions of the island of Reil and the lenticular nucleus, and in the white matter between the external portions of the lenticular nucleus.

According to Mills and Spiller, lesions restricted to the lenticula apparently do not cause sensory symptoms. Motor symptoms probably result from lesions situated in certain parts of the lenticula; speaking generally, the lenticula may be regarded as a motor organ. Anarthric or dysarthric speech disorders result from lesions of some portion of the left len-

ticula, which probably contains centers which are concerned with the movements which make speech possible. Destructive lesions of certain portions of the lenticula probably cause a paresis of the limbs or face; the paresis or paralysis caused by such lesions of the lenticula differs from that produced by capsular lesions, the impairment of power being so severe and not being so characteristic in the former as in the latter case; and from that produced by cortical lesions in that it is less likely to be dissociated; although dissociated lenticular paresis may occur.

While the diminution of power which results from a destructive lenticular lesion is permanent, it is usually not intense. Persistent true motor aphasia, as this form of speech disorder is generally understood, is not caused by a lesion restricted to the lenticula, no matter what its size or destructiveness. This insula, cortex, and subcortex play an important part in speech phenomena, one entirely different from that played by the lenticula and the internal capsule; the insula is a part of the cortical motor center for speech, Broca's convolution probably forming with the insula the entire cortical motor center for speech. Motor aphasia may be present without a lesion of the left third frontal convolution.

There is no inborn or preformed center for spoken or written speech corresponding or similar to the centers for motor functioning. The psychic processes are due to vibrations of the neurons which are propagated by a large number of cells, these in turn being roused to action by the initial volitional or reflex excitation. Experiences with thousands of soldiers wounded in the head during the war failed to reveal any instance of aphasia from a wound localized in the region of the third frontal convolution. It was the wounds of the left temporoparietal region, back of the fissure of Rolando, which were accompanied with aphasia. The brain that Broca used for his first demonstration of "Broca's aphasia" is still in the museum. The softening process was old and extensive, but Broca was misled by Gall's phrenology to

localize the seat of the aphasia in the frontal lobe as the point where the pathologic process had begun, disregarding all other parts of the brain. If an actual speech center existed, deafmutes would use some kind of speech, but we know that the sounds they make are less like speech than the sounds made by various animals. The deafmute has to be trained entirely from without. The infant shows also the absence of any congenital speech center.

Aphasia has never been known in a case of right hemiplegia that had developed in a young child. In learning to talk, the child uses other parts of its brain. The nerve elements of the left hemisphere develop a little earlier than the right hemisphere, and the first mental processes thus begin here and form, as it were, a crystallization center and a base for the association of ideas. Thus the brain uses this left hemisphere for an important part of its psychic activity, and specializes certain parts of it here, although there is no one special "center" for any of the psychic processes. The different cells of the brain join in a number of different psychic processes just as mathematicians use only 10 figures for the most complicated calculations. P. Marie (*Presse méd.*, Mar. 1, 1922).

In 2 cases of metastatic tumor nodules in the left hemisphere, P. Bailey (*Arch. of Neurol. and Psych.*, May, 1924) was enabled to determine the exact position of these nodules by reference to the schema drawn up by Pierre Marie and Foix on the basis of war experience. These observers recognize the following 5 zones;—

(1) *Zone of anarthria* (quadrilateral lenticular zone), disease or injury of which is manifested in: Dysarthria involving simultaneously intonation, articulation and rapidity of elocution. On attempting to speak, pronounced effort, premonitory hesitation and spasmodicity of speed. Aphasia slight,—mainly difficulty in reading, sometimes in writing and figuring.

(2) *Zone of the supramarginal gyrus*: Aphasia involving all the elements of speech (global). Hemianesthesia nearly always present, slight brachial monoplegia

usually, and bilateral ideomotor apraxia sometimes. No hemianopsia.

(3) *Zone of the angular gyrus*: Alexia predominant and almost absolute. Writing relatively unaffected. Speech comprehension and calculation impaired. No anarthria. Hemianopsia always present, sometimes as a quadrant defect.

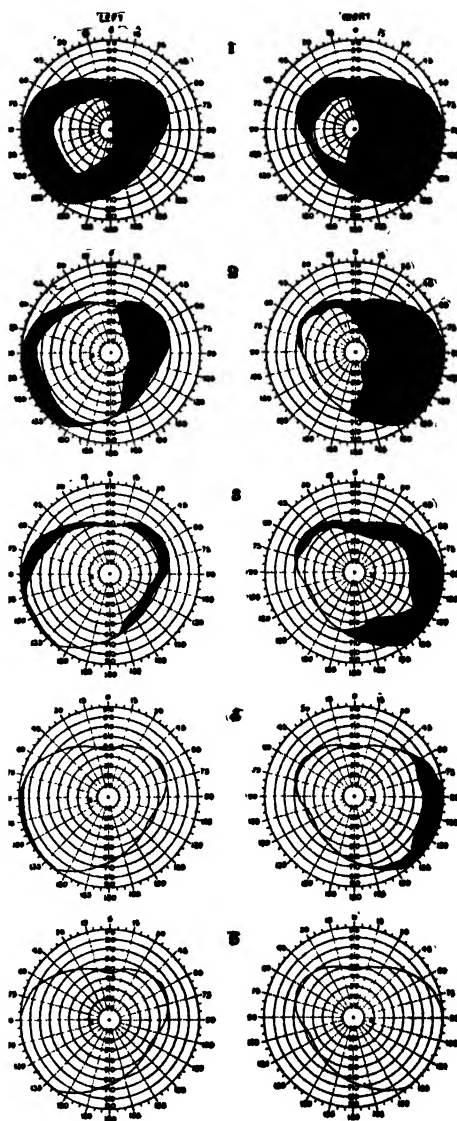
(4) *Temporal zone*: Aphasia affecting especially the naming of objects (loss of vocabulary). Comprehension of speech, reading, writing and calculation equally involved. Intelligence reduced. Anarthria practically absent. No hemiplegia. Hemianopsia present, often in quadrant form.

(5) *Zone of global aphasia* (involving chiefly the posterior central gyrus and partly the supramarginal and superior temporal gyri): General aphasia. Pronounced reduction of intelligence. Speech reduced to a few words, with comprehension only of the simplest orders. Reading, writing and calculation practically impossible. No apraxia. No hemianopsia.

Case of complete aphasia in which necropsy revealed a hemorrhage involving extensively the left lenticular nucleus and adjacent structures, with the third frontal convolution escaping entirely. Dercum (Arch. of Neurol. and Psych., Dec., 1924).

**Agraphia.**—True agraphia is generally ascribed to a lesion of the foot of the second left frontal convolution or of the subcortical fibers therefrom. It is usually associated with some form of motor aphasia.

**Sensory Aphasia.**—Cortical word-deafness is usually caused by a lesion of the middle or posterior portion of the first and second left temporal convolution, chiefly the first. Auditory speech is not, however, so exclusively a left brain function as is motor speech; hence the fact of incomplete and more transient types of speech-defect from unilateral lesions of this region. Lesions affecting the subcortical white fibers from this area give rise to the subcortical type of word-deafness.



Series of perimeter charts in a case of complete agraphia and almost complete word-blindness, with right-sided bilateral temporal hemianopsia. (The black area represents the blind parts of the fields.) Chart 1 represents the fields of vision on Nov. 17th. Chart 2 represents the fields of vision on Nov. 24th. Chart 3 represents the fields of vision on Dec. 1st. Chart 4 represents the fields of vision on Dec. 8th. Chart 5 represents the fields of vision on Dec. 15th. (Byrom Bramwell.)

Cortical word-blindness is caused by a lesion of the postero-inferior portion of the second left parietal convolution (angulo-occipital region).

Lesions affecting the optic radiations of Gratiolet cause the subcortical variety of alexia. Interruptions of relations through commissural fibers with any of the associated speech-areas will, of course, result in one of the mixed forms of aphasia or in subcortical alexia.

**PROGNOSIS.**—Functional aphasia associated with hysteria, migraine, epilepsy, fugitive edematous, or toxic states or from intracranial pressure (temporary) or shock, usually disappears promptly; aphasia from syphilitic thrombosis or endarteritis obliterans is also readily responsive to specific treatment. The prognosis is always better in young children than in those of adult life, as much may be accomplished by vicarious or compensatory education of the right brain.

Word-deafness may continue permanently, but it frequently improves through the co-operation of other sensory centers, and especially the visual center. The patient, noting the movements of the lips in those who are speaking to him, recalls motor images which articulation of the same words would require in him.

Word-blindness does not improve in some cases; in others a painstaking and early re-education may be carried out, by which new images may be created in the visual memory by the help of the motor and auditory memories.

Aphasia proper, or aphemia, occasionally remains the same from the beginning to the end, no improvement being visible; usually, however, words return very gradually. Recovery in such cases is never complete.

Some cases recover almost immedi-

ately. This almost always occurs in cases of complete aphasia, and would seem to be of dynamic origin, like the mutism of hysteria or of terrified persons.

Agraphia is in some cases recovered from in the sense that the patient learns to write with the left hand. The writing does not resemble that performed with the right hand, and in some cases it is written from right to left, as in mirror-writing.

Supracortical motor aphasia is less serious than cortical motor aphasia, because the intelligence is less affected, the center of language itself being intact and only the path of communication being interrupted.

Recovery occurs more frequently than in cortical motor aphasia.

**TREATMENT.**—When there is no paralysis present, mental overwork is a frequent cause of aphasia. Prolonged rest alone secures relief. Any disorder, concomitant or causative, that may be present should receive careful attention. At the same time the patient should be taught to overcome the aphasic symptom; considerable patience is usually required. When the aphasia is associated with right-sided paralysis or convulsions, the treatment of the latter condition by alteratives, **potassium iodide**, or **mercury** or **arsphenamin**, if a syphilitic taint be present, sometimes brings about rapid recovery.

Case of Déjerine's aphasia, pure motor or Marie's anarthria. The patient was a machinist, 48 years old, who suddenly developed paralysis of the entire right side of the body, with loss of the power of speech. Ability to read and to write both from dictation and from copy, however, remained. A positive Wassermann reaction being obtained, **arsphenamin** was introduced into a vein and active mercurial treatment instituted. Im-

provement in the symptoms speedily took place and articulate and intelligent speech gradually returned. F. X. Dercum (Med. Rec., Jan. 10, 1914).

The difficulty in finding the proper word in aphasia is much greater for names of unseen objects than for the visible. This should be borne in mind in training aphasics. F. Lotmar (Schweizer Archiv f. Neurol. u. Psych., Apr., 1920).

In re-educating cases of ataxic aphasia one should realize that the function of the muscles is not lost and that it will be regained when the attention is diverted so as to give them a chance for automatic co-ordinated action. The aim should be to restore the memory of the combinations of sounds which characterize words. Aphasia is less a loss of words than an inability to use them. The aphasic patient has neither the memory nor the attention to profit by abstract ideas, hence the teaching of **exercises** may have to be kept up for a year or more. Some member of the family or other patient person should carry them on daily. The methods, difficulties and results are like those obtained in training the mentally backward. Froment (Paris méd., Oct. 1, 1921).

Injury to the skull, especially when there is depression of the inner plate, tumors, cerebral hemorrhage, and other conditions capable of inducing cerebral pressure, requires appropriate surgical procedures.

Traumatic sensory aphasia, the writer states, is often due to subdural hemorrhage pressing on the cortical sensory speech centers. It affects the visual more than the auditory speech center. If treated expectantly, recovery is generally incomplete and there is a risk of epileptiform convulsions developing later. Treatment by **trephining** and **removal of the clot** is the best course. Cope (Brit. Jour. of Surg., Apr., 1914).

Case of motor aphasia in which the condition set in immediately after a stab wound at the foot of the 3d left fron-

tal convolution. Facial paralysis and other manifestations of hematoma appeared after 3 days, and were relieved by **decompression**. The aphasia retrogressed slowly after some months. Fiamberti and Filippini (Rif. med., Apr. 30, 1923).

Procedure yielding rapid results in the **re-education** of aphasics described. A man aged 36 had been struck on the left side of the head by an aeroplane propeller. Upon suitable surgical treatment, consciousness began to return, though with complete aphasia, and the hemiplegia partly retrogressed. Later, **scar tissue** was **dissected out** on account of epileptic seizures, and an **inlay bone graft** from the tibia implanted. The subsequent occasional seizures were controlled by a daily dose of 5 grains (0.3 Gm.) of **phenobarbital**. The patient was told to think of himself as learning to speak again and to note his constant improvement. His wife's aid was enlisted to help him practice, read to him and cheer him. Deep breathing, auditory practice, importance of the vowels, inflection and use of the face muscles was emphasized. **Speech re-education** began with diaphragm breathing and counting, together with explanation of his difficulty in making the wide "e" and "eh" sounds. After a week's training in counting, he could count perfectly. Sums in addition and subtraction followed, with vowel practice combined with consonants, and singing the vowel sounds up and down the scale. Consonants difficult to pronounce were thoroughly practised with special words embodying them. Then followed rhymes and poems, measurements, money, writing with both hands, etc. The patient was thus greatly improved, being enabled to copy words, read words, say words and sentences, and express all things intelligibly, if unhurried. The voice gained in volume. C. G. Stivers (Jour. Amer. Med. Assoc., Oct. 20, 1923).

WM. BROADDUS PRITCHARD,  
New York.



**APIOL** is obtained from the volatile oil of parsley. At low temperatures apiol is a stearopten or camphoraceous solid made up of needle-like crystals which, at higher temperatures, resolves itself into a yellow or straw-colored liquid. It has a slightly acid reaction and is soluble in alcohol, ether, and chloroform. Most of the apiol of commerce is nothing but an oil of parsley. It may be prepared in various ways, but the methods of manufacturers as published are usually obscure. Green apiol is the oil of parsley loaded with chlorophyll and vegetable fats.

The product of this class most used in therapeutics at the present time is the French *apioline*, "made by exhausting the seeds of *Apium petroselinum* with light petroleum, distilling, washing with alcohol, and treating the washings with caustic soda, which yields the pure apioline on distillation." It is a reddish liquid.

**DOSE.**—Owing to its unpleasant odor and acrid taste, apiol is best administered in gelatin capsules or perles, each holding from 3 to 5 minims (0.2 to 0.3 c.c.). Two to 4 capsules may be taken daily, preferably night and morning, beginning two or three days before the expected menstrual flow. Apioline is available in 20-cg. (4-minim) capsules; 2 or 3 may be given daily at intervals of from three to six hours to relieve pain or bring on the menstrual flow.

**PHYSIOLOGICAL ACTION.**—Apiol is thought mainly to act upon the vascular system, causing congestion, and at the same time on the muscular tissue of the uterus. This view is based upon its action as an emmenagogue and by its effects upon the menstrual flow; yet, it is also a regulator of uterine function. It causes, in large doses, cerebral excitement similar to that caused by coffee, with tinnitus, vertigo, and violent headache. Apiol provokes toxic phenomena when used as an abortifacient, *i.e.*, in excessive or very large doses.

Case of poisoning in a woman aged 28, pregnant two and a half months, who took 10 capsules of apiol with the intention of producing abortion. A similar dose was taken in the morning, and, as no result followed, 10 more on the evening of the following day; thus

6 Gm. were taken within forty-eight hours. No symptoms were produced till soon after the third dose, when she began to suffer from severe vertigo which compelled her to lie down, which was soon followed by nausea and vomiting which continued all night. In the morning she observed that her face was red and swollen, the vertigo and vomiting persisted, and were accompanied by diarrhea. At the same time a generalized eruption appeared, for which the writer was summoned, on the third day of the illness. He found an extensive urticarial eruption covering the face, neck, and anterior surface of the chest and abdomen. It was also present on the inner and anterior surfaces of the thighs, legs, and arms, but the extensor area of the limbs was but slightly affected. The face was red and swollen, and the surfaces affected were very itchy. There was slight jaundice, and the liver was large and tender. The urine was scanty and high colored, but without the presence of albumin. The vulva was the seat of considerable edema, but absolutely no action was observed on the uterus and the progress of the pregnancy was unaffected. Under milk diet and a simple diuretic all the symptoms gradually disappeared in the course of a few days. Glatard (The Medical Review; Antiseptic, May, 1911).

**THERAPEUTICS.**—According to Griffith and Cerna, apiol (apioline) may be regarded as the best emmenagogue known. It is indicated in **amenorrhea** due to anemia from whatever cause.

According to Dorland, however, the drug, in order to insure the best results, should be combined with some preparation of iron; he also suggested that iron be given uninterruptedly until a few days before the expected appearance of the menses. Then, continuing the iron, apiol may be prescribed in 5-minim (0.3 c.c.) doses, two or three times a day, until the appearance of the menstrual discharge. Apiol is also helpful in **congestive dysmenorrhea** unless this be due to mechanical obstruction; relieving the pain and increasing the flow if this is insufficient.

S.

**APOCYNUM** is the dried root of *Apocynum cannabinum* Linné, also known as American hemp, Indian hemp, dogbane, and Canadian hemp. The plant is native to North America, grows to a height of 6 feet at most, and produces light-greenish flowers. The part used, the root, occurs in commerce in brownish, bark-covered pieces varying from  $\frac{1}{8}$  to  $\frac{1}{3}$  inch in diameter. It contains, besides tannic acid, gallic acid, and gum resin, an active principle which has been termed by Finnmöre *cynotoxin* and isolated by him in 1909 as a neutral crystalline bitter substance. In 1913, however, Impens renamed the active principle *cymarín*, and it is now generally known by that name, or as coumarin or coumarin.

#### PREPARATIONS AND DOSE.—

There has been no official preparation of apocynum since the 8th Edition of the Pharmacopœia, in which it was recognized in *Fluidextractum apocyni*, prepared from the powdered root. The dose is 5 minims (0.3 c.c.) when the cardiorenal therapeutic action of the drug is to be utilized and 15 minims (0.9 c.c.) to produce emesis. It should not, however, be used for the latter purpose if other emetics are available, since such doses tend to produce gastrointestinal irritation.

The active principle, *cymarín*, is commercially available, and may be used intravenously for a few days in a daily dose of from  $\frac{1}{180}$  to  $\frac{1}{60}$  grain (0.00035 to 0.001 Gm.). The initial dose by mouth is  $\frac{1}{200}$  grain (0.0003 Gm.), to be gradually increased if well borne.

Coumarin, a new glucosid of apocynum cannabinum was tested by the writer, on animals. He concluded that it is an active cardiac tonic similar in action to drugs of the digitalis

group. V. D. Zelensky (Roussky Vrach, Jan. 25, 1914).

The writer tried coumarin in 30 cases. Its use intravenously in doses of 0.0005 Gm. ( $\frac{1}{20}$  grain) to 0.001 Gm. ( $\frac{1}{4}$  grain) every second day until about 0.0065 Gm. ( $\frac{1}{10}$  grain) had a good effect on the heart and diuresis, but it cannot replace digitalis, although occasionally efficacious where digitalis has failed. It is not followed by untoward symptoms, has no cumulative action, and does not disturb sleep. M. R. Bonsman (Deut. med. Woch., Jan. 1, 1914).

#### PHYSIOLOGICAL ACTION.—

As emphasized by A. A. Woodhull many years ago, the powerful emetic and cathartic effects which the dispensatory—and various textbooks, we may add—have attributed to the root of apocynum resulted from its unintelligent use, the characteristic effects of the drug, when employed in appropriate doses, being those of a diuretic and cardiovascular stimulant. Hence its frequent classification in the digitalis group.

As a *diuretic*, apocynum earned from Dr. Rush early last century the title of “vegetable trocar” owing to its activity. According to Woodhull, in fact, it seemed to have no exact equivalent either in thoroughness or in promptness of action. Under its use Dabney noted that 1 to 2 gallons of urine were passed daily. This action has been attributed to the fact that apocynum increases the contractile power of the cardiac and vascular muscles in therapeutic doses, and in this manner enhances the excretory activity of the renal filter.

Sokoloff, Wood, Jr., and others found that if a small quantity of apocynum is injected into the vein of a dog a marked slowing of the pulse occurs, usually accompanied by a

very considerable rise of blood-pressure. This action is soon followed by free diuresis. Rose Bradford found that apocynum did not irritate the renal epithelium.

Its action as a *cardiovascular stimulant* is uniformly compared to that of digitalis, even to the possession of its defects: the production of nausea and gastric irritation. It is believed to stimulate the heart muscle and the vessels directly, the view that the cardiovascular phenomena are due exclusively to excitation of the bulbar centers having been found invalid in view of the fact that division of the spinal cord failed to prevent the physiological effects of the drug. Under the influence of the remedy there soon occurs slowing and increased force of the pulse. It tends also to control arrhythmia and to augment the respiratory amplitude.

The vasoconstrictor action of apocynum is considerably more powerful than that of strophanthin; its action on the heart is slightly weaker than that of the latter. On the other hand, it is excreted or destroyed with comparatively rapidity, and there is experimental basis for the statement that it is not cumulative in its action. The question whether it is excreted or destroyed within the body remains open for the present. It is thought that the employment of the pure active principle should eliminate the drawbacks which have hitherto restricted the use of this drug, for these are probably due to the presence of other constituents of an irritant nature in the crude extracts. The rapidity with which cynotoxin acts enjoins caution with respect to subcutaneous dosage. Dale and Laidlaw (Post-Graduate, Dec., 1910).

Cymarín was found by the writer to be a rapidly acting cardiac stimulant, best given intravenously. It is a true diuretic with a selective action

on the renal cells. A. Soldano (*Semana Medica*, June 10, 1915).

In experiments on dogs, in which cymarín was injected intravenously, the writers observed the expected slowing of the heart rate by central and peripheral vagus stimulation, but could not confirm the increased tone of the heart-muscle, which was, instead, decreased. There was general vasoconstriction, which included the kidneys, thereby hindering urinary excretion. Beco and Dossin (*Bull. de l'Acad. roy. de méd. de Belg.*, xxix, 1184, 1919).

**POISONING.**—The drawbacks of this drug, which, though active, is but little used, arise partly from the injudicious doses sometimes administered. Any dose above 5 minims (0.3 c.c.) tends to produce violent nausea, vomiting, and intestinal disturbances. Sokoloff found experimentally that a toxic dose first produced a pronounced rise of the blood-pressure, and that this was followed by a paralyzing effect on the vasomotor center, the blood-pressure gradually falling to zero. In mammals the heart is stopped in systole, according to Rose Bradford, though a massive dose may stop it in diastole. In man, poisoning tends to be prevented by the emetic action of an overdose.

The *treatment* of apocynum poisoning, were such met, would be similar to that for digitalis, viz., **evacuation of the stomach**, and vasodilators, such as **veratrum viride**, the inhalation of **amyl nitrite**, **nitroglycerin** hypodermically, and the use of **saline solution** at 105° F. intravenously to dilute the blood and favor the passage of plasma into the lymphatic channels.

**THERAPEUTICS.**—The marked activity of apocynum as a diuretic

renders it available in the treatment of **dropsy**, whatever be its cause. The fact that it does not irritate the renal epithelium, notwithstanding its prompt and efficient action and the fact that, unlike digitalis, it is not cumulative, makes it possible, it has been claimed, to use repeated small doses of apocynum in place of the trocar for the purpose of securing eliminative effects. Not only is the operative procedure avoided, but the fluid eliminated is not pure blood-serum, as is the case with the trocar, but true products of excretion eliminated through the physiological intervention of the renal filter. Again, apocynum, even in small doses,—5 minims (0.3 c.c.) or less of the fluid-extract, repeated as needed, three or four times daily,—also enhances intestinal activity for the elimination of fluids—a feature which tends to increase its efficacy in the treatment of **hepatic cirrhosis**, and in **Bright's disease** where this derivative action is desirable. In the edema of **heart lesions**, especially those attended with defective compensation, the drug is of some value owing to its digitalis-like action on the heart muscle.

Apocynum has not taken the rank it deserves in **Bright's disease**. This is because inferior preparations are frequently dispensed. The writer has used the fluidextract in capsules, thus avoiding the nausea so frequently attending the administration of the drug. In a case of mitral regurgitation with inflammation of the kidneys, which had been treated in the usual way by cardiac tonics, baths, and uva ursi, the patient's urine had fallen to 6 ounces in twenty-four hours. The fluidextract of apocynum cannabinum was begun in 8-drop (0.5 c.c.) doses every four hours. Within the next twenty-four hours the urine had increased to 132 fluid ounces, and for a

week the amount varied from 130 to 160 ounces. The edema disappeared, and the average pulse rate fell from 116 to 92, and its quality was improved. Under the use of the drug the distressing dyspnea disappeared. No permanent benefit was to be expected in a case as severe as this, but the symptomatic improvement was very marked and the comfort of the patient enhanced. R. R. Paine (St. Louis Courier of Medicine, Jan., 1903).

The cardiac disorders in which its efficiency has been found greatest include in particular **mitral** and **aortic insufficiency** with disturbed compensation. The cardiac impulse becomes stronger, the pulse fuller, more regular, and slower. The blood-pressure rising, the dyspnea and cyanosis, if any be present, disappear.

Series of personal cases of **chronic cardiac insufficiency** in which digitalis had failed and apocynum yielded benefit. The action is similar to that of digitalis, though not so durable; when digitalis is contraindicated or has ceased to improve, apocynum may prove advantageous. Fehsenfeld (Münch. med. Woch., Jan. 17, 1911).

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

**APOMORPHINE.**—Apomorphine is an alkaloid obtained by the action of HCl or some other acid or dehydrating agent on morphine, causing each molecule of the latter to lose a molecule of water. A white powder soluble in hot and cold water is formed, a watery solution of which, though colorless at first, soon turns black.

The salt generally employed is the hydrochloride (*apomorphinæ hydrochloridum*), made by adding a small quantity of hydrochloric acid to a solution of apomorphine.

**PROPERTIES.**—This salt occurs in small, grayish-white, acicular crystals, which are odorless and slightly bitter and become green on exposure to light and air. The Pharmacopœia directs that the salt be rejected if it at once imparts an emerald-green color to 100 parts of distilled water when shaken with it in a test-tube. For hypodermic use reliable tablets extemporaneously dissolved are still better. The hydrochloride is soluble in about 40 parts of water or alcohol. It should be kept in dark amber-colored bottles to avoid the decomposing action of light.

**DOSE.**—The dose for adults ranges from  $\frac{1}{60}$  to  $\frac{1}{8}$  grain (0.0011 to 0.008 Gm.);  $\frac{1}{10}$  grain (0.0065 Gm.) hypodermically suffices to produce emesis. Great care must be observed in using apomorphine in feeble persons. Death has been caused by  $\frac{1}{15}$  grain (0.004 Gm.) under such circumstances. In the case of a drunkard reported by Westby,  $\frac{1}{10}$  grain (0.0065 Gm.) of apomorphine, hypodermically administered, followed in five minutes by  $\frac{1}{40}$  grain (0.0016 Gm.) more, caused collapse, unconsciousness, cold surface, and absence of pulse at the wrist. For a child of 18 months,  $\frac{1}{100}$  grain (0.00065 Gm.) may be used; at 2 years  $\frac{1}{80}$  grain (0.0008 Gm.) at 3 years  $\frac{1}{70}$  grain (0.0009 Gm.) at 5 years  $\frac{1}{60}$  grain (0.0011 Gm.), and at 8 years  $\frac{1}{50}$  grain (0.0013 Gm.).

One-fifth grain (0.013 Gm.) should not be exceeded in any strong adult case when given hypodermically, and  $\frac{1}{8}$  grain (0.008 Gm.) when administered by the mouth.

**MODES OF ADMINISTRATION.**—When used as an emetic, apomorphine is given hypodermically in 1 per cent. solution; where employed for

its expectorant properties, it is administered *per os* in small doses, such as  $\frac{1}{30}$  grain (0.0022 Gm.).

The drug acts with more vigor in some individuals than in others. Its effects, therefore, should be closely watched. As stated by Murrell, apomorphine, when administered on an empty stomach, produces vomiting much more readily than when administered after a meal. The rate of absorption has much to do with the entire effect. When given hypodermically, the drug is absorbed at once; when given on an empty stomach, it is absorbed more rapidly than when mixed with food.

**INCOMPATIBILITIES.**—Apomorphine hydrochloride is incompatible with alkalis, tannic acid, ferric chloride, potassium iodide, and silver nitrate.

**CONTRAINDICATIONS.**—As an emetic, apomorphine is contraindicated, in common with other agents of this class, in cases with pronounced cardiac or vascular weakness, *e.g.*, in the presence of advanced degenerative changes in the heart or of aneurism or atheroma, the rise of blood-pressure induced by vomiting being attended with danger to the integrity of the circulatory organs. Similarly, in cases of poisoning by caustics the use of apomorphine is inadvisable, for obvious reasons. In all conditions of marked general weakness, *e.g.*, in the late stage of poisoning by various drugs, especially narcotics and depressants, the muscular exertion attending the act of vomiting may induce collapse. In all stages of morphine or opium poisoning apomorphine is contraindicated because of the comparatively close relationship existing between it and morphine and the consequent tendency it manifests to add to the general depression caused by the narcotic. Hernia, advanced pregnancy,

pulmonary tuberculosis, and gastric ulcer also contraindicate the use of apomorphine as an emetic.

The consensus of opinion at the present time is that apomorphine is too depressing for children when given in sufficient doses to produce emesis, though valuable in them in spasmodic disorders, *i.e.*, when it can be administered in very small doses.

The doses usually recommended in textbooks are too large. The writer's dose for an adult is  $\frac{1}{20}$  grain (0.003 Gm.). This will usually produce the emetic and relaxing result desired, and if it does not it can be repeated. A dose of  $\frac{1}{15}$  grain (0.004 Gm.) should be the maximum, and given then only in desperate cases of poisoning. The writer witnessed toxic effects from  $\frac{1}{10}$  and  $\frac{1}{15}$  grain. The drug should be used only as a last resort in children. F. K. Boland (Atlanta Jour. Rec. of Med., Aug., 1908).

In dogs the evidence in favor of the existence of a central controlling mechanism for the act of vomiting is conclusive; apomorphine acts solely by direct stimulation of this mechanism probably also in man. There is no valid evidence in favor of a local reflex action of this drug.

After intravenous and intramuscular administration no apomorphine was found in the vomitus. This was proven by an ingenious method. A large dog was given the drug several times intravenously, each dose sufficient to produce emesis. The vomitus was collected, evaporated to a small bulk and injected into a much smaller dog with no signs of vomiting; suitable doses of apomorphine had produced emesis immediately preceding and following the injection of the vomitus. After a single large intramuscular injection no apomorphine was found in the vomitus by a similar test. Finally, apomorphine can produce all the symptoms of vomiting (excepting of course the actual expulsion of the gastric

contents) without the presence of a gastrointestinal tract. This was proven by excising the stomach and intestines without development of shock and in such animals the salivary and muscular phenomena "proceed exactly as in the normal animal, so that we can say unhesitatingly that no one who might see a normal dog and an eviscerated one vomit could distinguish the normal from the eviscerated animal so far as the vomiting act is concerned." They have also shown, by the same method, that the emetic action of the digitalis substances is central; this experiment has been confirmed in the laboratory. Eggleston and Hatcher (Jour. of Pharmacol. and Exper. Therap., May, 1912).

#### PHYSIOLOGICAL ACTION. —

The administration of  $\frac{1}{10}$  grain (0.0065 Gm.) hypodermically is followed in scarcely one-half minute by fullness of the head; the pulse is quickened and increased in volume; the pupils slowly dilate; the face is flushed. Perspiration soon appears; the respiration and heartbeats become more frequent; there is more or less depression and muscular weakness, and before two minutes elapse emesis is produced, which may recur three or four times within fifteen or twenty minutes. Then comes the reaction, a general relaxation, lasting about an hour. The eyes are sunken, the pupils are widely dilated, and the face is pallid and drawn. Yawning inaugurates the period of recovery; sleep follows, and, upon awakening, all the effects have passed away.

Series of experiments on derivatives of apomorphine. The most marked physiological actions of apomorphine are two: a paralyzing action exerted on the motor portion of the cord and on the muscles, and an excitation of the vomiting center in the brain, resulting in nausea. In their recent experiments the writers were surprised to discover that it had almost none of the toxic

action which Harnack had previously found, although its action on the vomiting center was the same. Frogs could be killed only by enormous doses or by immersion in solutions of apomorphine. These differences cannot be explained by the presence of impurities in the earlier preparations. There may exist some isomeric forms of apomorphine. Harnack and Hildebrandt (Archiv f. exper. Pathol. u. Pharmacol., Bd. lxi, Hft. 4, 1909).

Salivation and an increase in the nasal and bronchial secretions, lachrymation, and diaphoresis are obtained with small doses of apomorphine, such as  $\frac{1}{30}$  to  $\frac{1}{25}$  grain (0.0022 to 0.0027 Gm.). Vomiting produced by larger doses is believed to be due to direct stimulation of the bulbar vomiting center. This is shown by the fact that vomiting occurs at once when a solution of apomorphine is applied to the medulla, and also by the relative promptness with which this symptom occurs when the drug is so administered as to cause it to reach the medulla promptly, i.e., by hypodermic injection, as compared to its action when given by the mouth. Ligation of the stomach vessels prevents the emetic action of apomorphine given by the mouth, but does not interfere with its action when introduced into the general circulation.

Experimental administration to animals such as the rabbit, guinea-pig, and other herbivora throws little light upon the physiological action of apomorphine in man, the symptoms produced being totally different—great restlessness and excitability—owing to the inability of these animals to vomit. In dogs the drug causes circus movements, the animals running in a circle; after large doses, there follow tetanic convulsions, and death ensues from respiratory arrest, the heart continuing to beat a brief period thereafter.

Apomorphine has a less conspicuous depressant effect on the brain-centers than morphine. It is not excreted into the gastrointestinal tract. Apomorphine is probably decomposed in the blood and tissues.

Study of the action of apomorphine, morphine and codeine as shown by perfusion of the medulla of the terrapin, usually with solutions of 0.01 per cent. strength. Apomorphine hydrochloride in fresh solution first stimulates then depresses the medulla; known stimulants fail to act after it has been used. Old solutions of a dark green color have no effect. Morphine sulphate stimulates and sensitizes the cardioinhibitory center, later depressing it. Codeine phosphate exerts no influence *per se* on the medulla, but when oxidized with nitric acid it stimulates the cardioinhibitory center more powerfully than either morphine or apomorphine. Heinekamp (Jour. of Lab. and Clin. Med., Dec., 1922).

### APOMORPHINE POISONING.

In the human being toxic doses of apomorphine produce unconsciousness, failing circulation and respiration, all accompanied by profound depression and marked weakness, which may pass into alarming collapse. Delirium and convulsions are sometimes observed.

A dose of apomorphine administered subcutaneously caused in the writer severe vomiting, associated during the final act with intense muscular relaxation, such that he had to lie for about half an hour unable to lift a finger or summon aid. Harnack (Münch. med. Woch., Sept. 8, 1908).

**TREATMENT OF APOMORPHINE POISONING.** — The most effective agent to counteract this condition is **strychnine**, but it should be supplemented by the more diffusible stimulants, as **ammonia**, **whisky**, **coffee**, etc., together with **external heat**.

**THERAPEUTICS.**—The pronounced value of apomorphine as an emetic is based mainly upon the facts that the average period of time elapsing before the occurrence of emesis is much shorter than that preceding the effect of other emetics, and that its action occurs best after hypodermic administration, thus permitting its employment even when the patient cannot swallow. For good results, it is essential that a pure specimen of the drug be available.

Apomorphine is mainly used, though less than formerly, in the treatment of **acute poisoning** by various drugs or other toxics—gastric lavage, however, being always preferable—when there is any likelihood that some of the poison is still present in the stomach. Occasionally it may be necessary to administer  $\frac{1}{10}$  grain (0.0065 Gm.) every ten minutes until some effect is obtained, or exhibit  $\frac{1}{4}$  grain (0.016 Gm.) at a single injection. In feeble persons and in children, however, great caution must be exercised. In poisoning due to narcotics or to depressants, such as aconite, veratrum, corrosive sublimate, arsenic, etc., apomorphine not only fails at times to produce emesis, but the added depression its use entails is fraught with considerable danger.

When given by mouth the effects of apomorphine differ widely from those obtained by its hypodermic use. Hypodermically it is a most valuable centric emetic in doses of from  $\frac{1}{20}$  to  $\frac{1}{60}$  grain (0.003 to 0.001 Gm.), acting quickly and gently. The possibility of depressing effects should be borne in mind when it is given to children, and strychnine should be combined with it. By mouth it has little emetic effect, but acts as an efficient expectorant in doses of  $\frac{1}{8}$  grain (0.008 Gm.) every two hours. It does not increase the effect of other narcotics.

It should not be used when there is abundant expectoration. Crystalline apomorphine is to be specified, since the amorphous form is uncertain in its effects. E. L. Fisk (Med. Rec., Sept. 28, 1907).

In **strychnine poisoning** apomorphine has been reported effective as a sedative. Thus, Horsley witnessed a case in which apomorphine, in doses of  $\frac{1}{15}$  to  $\frac{1}{10}$  grain (0.004 to 0.0065 Gm.) subcutaneously injected, completely subdued the convulsions, and eventually successfully antagonized the excitant alkaloid.

Apomorphine emesis is sometimes helpful when a **foreign body** has lodged in the **esophagus** or in the **pharynx**, the act of vomiting being the expelling agent.

Apomorphine hydrochloride has also been recommended in **cerebral congestion** when it is desirable to empty the stomach quickly. But it should rather be avoided in aged subjects suffering from this condition, owing to the violent rise of blood-pressure which the act of vomiting provokes. Gastric lavage is preferable in such subjects.

It acts as an expectorant and sedative in doses ranging from  $\frac{1}{80}$  to  $\frac{1}{20}$  grain (0.0008 to 0.0032 Gm.). As such it affords great relief in cases of **bronchitis**, **tracheitis**, and **catarrhal pneumonia**. It has been used advantageously by Arnstein in **laryngeal diphtheria** when the swelling and softening of the false membrane after antitoxin injections cause signs of suffocation. A hypodermic dose of  $\frac{1}{2}$  grain (0.0054 Gm.) induces vomiting and clears the larynx.

A spray of apomorphine in weak solution is sometimes recommended, but the use of the drug in this manner is



hardly safe. It has been found valuable in **whooping-cough** to relax spasmodic attacks (Ingram).

Murrell recommends that apomorphine be given in large doses as an expectorant in **bronchitis**. He obtained excellent results from an ointment of: apomorphine, 1 grain (0.065 Gm.); lard or lanolin, 1 ounce (31 Gm.). One-half of this is rubbed into the chest. Murrell also observed the expectorant effect in many by using apomorphine as a spray; it was very marked when the drug was used in large doses. A dose which would act as an emetic, if administered hypodermically, could be used as an inhalation without giving rise to this result. To offset the depressing effects, strychnine may be used.

Apomorphine hydrochloride has received much praise as a soporific in **insomnia**,  $\frac{1}{30}$  grain (0.0022 Gm.) being administered hypodermically on retiring. It has been extensively used for this purpose in **acute alcoholism**. In this condition it should be given in a single dose, likewise of  $\frac{1}{30}$  grain (0.0022 Gm.), injected subcutaneously. The object is to give a dose that is large enough, on the one hand, to produce sleep, and, on the other, is sufficiently small so that nausea and vomiting are avoided. Hence, individual susceptibility must be considered. The drug should be given when the patient is in bed, for its effect is very rapid and the patient will usually fall into a restful sleep within five to twenty-five minutes. If no results are observed within one-half hour the dose is too small.

Apomorphine is probably the most useful single drug in the therapeutics of **alcoholism** and in some other drug habits, especially morphinism. No other acts so promptly and certainly.

In maniacal drunkenness or in any form of drunkenness with excitement, the effect of a full dose of 20 minims (1.25 c.c.) of a 1:200 solution, given hypodermically, is dramatic. A wildly uproarious patient, requiring restraint by 2 or more attendants, is quietly asleep in 10 minutes, in fact usually less. Given in the full dose the drug is always strongly emetic, but the vomiting is short-lived. The hypnotic effect is no less certain and hardly less rapid. In some few cases the patient is fast asleep before the intermittent spasms of the diaphragm have ceased. If, as is possible, the vomiting has not quite emptied the stomach, there may be a danger of asphyxia if the patient be left alone too soon. The further course of the case depends upon the amount of alcohol which has been absorbed before the stomach was emptied by vomiting. The apomorphine sleep itself does not last more than an hour or so, but it may start a sleep which is carried on by the alcohol already absorbed; thus, the total sleep may last 7 or 8 hours, and the patient awake sober. If the sleep lasts only an hour or two, he is invariably quiet and easily managed when he wakes, even if not sober.

During the premonitory stages of **dipsomania** or during the paroxysm, apomorphine is the most useful drug, in spite of its usual evanescent action and the necessity for frequent repetition. In the premonitory stage, indeed, the effect may be much more enduring, as in a case seen by the author in which a single small injection of 5 minims (0.3 c.c.) was always enough to defer a whole paroxysm. Where drinking has already commenced, injections of 5 minims may have to be repeated several times daily.

In that variety of the **insomnia** in which the patient finds himself wide awake as soon as he lies down in bed, although he may have felt drowsy all evening, small doses of 4 or 5, up to 8 minims (0.25 to 0.5 c.c.) are very effective. If a patient can go to sleep but wakes after a few hours, the drug

will have to be administered at this time. Apomorphine does not set up any craving; no patient ever has any desire to continue its use, and obviously the danger of his increasing the dose would be prevented by the emetic action of the drug. Its continual use in small doses does not prevent the patient from sleeping moderately well when it is discontinued; this would not be the case with any other hypnotic. Apomorphine acts very efficiently in the insomnia following **morphinism**. Francis Hare (Practitioner, Oct., 1924).

In laryngeal disorders attended by laborious and suffocative breathing and spasm, known as "**croup**," whether simply catarrhal or membranous (not diphtheritic, since here antitoxin should at once be given),  $\frac{1}{400}$  or  $\frac{1}{60}$  grain (0.00065 or 0.0011 Gm.) every fifteen minutes produces a happy effect. As relief comes, the interval is lengthened to one or two hours. The same sedative property has enabled apomorphine to allay **spasmodic asthma** and to curtail paroxysms of **pertussis**. When amyl nitrite or other nitrite is not available, apomorphine may be useful in **angina pectoris**.

From the fact that this alkaloid produces emesis by the action through the medullary nerve-centers, and not by irritation of the mucous membrane, it is a good remedy where an emetic is indicated in **catarrhal gastritis**, *i.e.*, when this disorder is due to the presence of toxic food materials, and washing out of the stomach—a better procedure in general—cannot, for some reason, be practised. It is also useful in very small doses in the **persistent vomiting** of gastrointestinal disorders.

The value of apomorphine hydrochloride in violent **gastralgia** is attested by Morris, the dose given to produce emesis being used. Balm

also found it efficient in a case of persistent **hiccough**. Tull used it with success in **chorea**, a single dose of  $\frac{1}{40}$  grain (0.0016 Gm.) causing cessation of the choreic movements; the benefit was kept up by the oral administration of  $\frac{1}{30}$  grain (0.0022 Gm.) every 3 hours.

Apomorphine hydrochloride has been employed for the relief of various **minor hysterical manifestations**. The amounts used varied from  $\frac{1}{8}$  to  $\frac{1}{20}$  grain (0.008 to 0.0032 Gm.), hypodermically administered, and were never followed by any alarming symptoms (Horsley). Foucher injects  $\frac{1}{15}$  to  $\frac{1}{40}$  grain (0.004 to 0.0065 Gm.) hypodermically before the onset of and during the paroxysm. It has been found of value as antispasmodic and diaphoretic in **puerperal eclampsia** by Kitchens, a result readily accounted for by the muscular relaxation, including that of the vascular muscles, to which the drug gives rise.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

**APOTHESIN.**—This locally anesthetic agent is, chemically, diethyl-amino-propyl cinnamate hydrochloride. It is soluble in water, and, in general, its properties resemble those of procaine.

For anesthesia by injection, solutions of 1 to 2 per cent. strength are generally used. In spinal anesthesia, solutions of 2.66 to 4 per cent., to the amount of 2 to 3 c.c. (32 to 48 minims), are injected. Over mucous membranes, 1 or 2 per cent. solutions are employed, although in the eye, where toxicity is less of a factor than elsewhere on account of the small amounts of solution instilled, solutions up to 4 per cent. are used.

The uses of apothessin correspond rather closely to those of procaine, although the drug has never achieved such widespread popularity. The drug is relatively safe. Meeker and Frazier, however, in experi-

ments on rabbits in which procaine and apothecin were injected intravenously in 0.5 per cent. solutions in 0.45 per cent. sodium chloride solution without adrenalin, found the lethal dose of apothecin smaller than that of procaine. Severe collapse has been recorded from injections of 1 and 2 per cent. solutions of apothecin in throat operations.

Apothecin withstands boiling without any appreciable loss of activity, is free from irritating action, and is compatible with adrenalin.

Apothecin employed in spinal anesthesia because it is 6 times less toxic than cocaine, recovery from toxic doses is prompt, and it has little effect on the motor cells. Prepared tablets containing apothecin,  $\frac{3}{8}$  grain, and adrenalin,  $\frac{1}{4000}$  grain, are used. Two tablets are dissolved in 3 c.c. of distilled water, making a 2.66 per cent. solution, for operations below the umbilicus, and 3 tablets, making a 4 per cent. solution, for operations above the umbilicus. Sterilization is effected by bringing the solution to a boil 6 or 8 times, since continuous boiling would decompose the adrenalin. D. A. Orth (Amer. Jour. of Surg., Jan., 1925). S.

**APPENDICITIS.—DEFINITION.**—An inflammation of the vermiform appendix, frequently complicated with ulceration and perforation of its coats, caused by microbic infection, but which may also originate from irritation produced by hardened fecal masses, foreign bodies, or traumatism.

Two forms of appendicitis, the *acute* and *chronic (relapsing or recurrent)*, are now generally recognized.

The writer calls attention to a group of cases in which, though the appendix is a factor, the chief irritative lesions are fibroid degeneration and syncongestive appendicitis. A second, larger group, with symptoms in the appendix region, but not including the appendix, appears to depend upon a variety of spinal irri-

tative lesions, with efferent impulses sent out both to the cerebrospinal nerves and sympathetic nervous system, and possibly to the automatic centers.

Pressure at a point about  $1\frac{1}{2}$  inches to the right of the navel and a trifle below, deeply enough to bring out the response from the right group of lumbar sympathetic ganglia, affords definite evidence that one is to look to the appendix for the source of irritation, provided the left group of sympathetic lumbar ganglia is not hyperesthetic. This point of tenderness situated several inches away from McBurney's point relates to a chronic irritative lesion of the appendix. Surgical judgment in addition requires one to determine if the patient is one with neurasthenic habit and relaxation of peritoneal supports with chronic enteric toxemia. R. T. Morris (N. Y. Med. Jour., May 20, 1916).

## ACUTE APPENDICITIS.

**SYMPTOMS.**—Whether catarrhal or ulcerative, the attack presents itself usually in a previously healthy person and begins with sudden intense pain in the abdomen, often beginning in the region of the umbilicus, and later localized in the right iliac fossa at a spot  $1\frac{1}{2}$  to 2 inches from the anterior superior spine of the ilium toward the umbilicus (McBurney's point), and increased by pressure. At first paroxysmal, it becomes constant. This is the most important diagnostic sign when associated with the other symptoms.

The characteristic aching or pain begins in the epigastric or umbilical region and spreads over the entire abdomen in 2 or 3 hours.

Then, in 6 to 12 hours from the onset, it settles or localizes in some definite area, usually in the McBurney region. J. E. Rawls (Va. Med. Mthly., June, 1925).

The pain may radiate from this point toward the umbilicus, the epigastrium, the groin, and the testicles. It may be felt in other parts, elsewhere on the right side of the abdomen, the pelvis, loin, or on the left side, and may even be located in the left iliac fossa. It is important to bear in mind, moreover, that, as stated by Sturm Dorf: While it is true today, as it was thirty years ago, that a typical McBurney point may be present in a typical appendicitis, it is equally true that appendicitis may exist in the absence of a McBurney point, and, most important: a typical McBurney point may be present in the absence of appendiceal involvement.

Pressure on the corresponding point on the opposite or left side will elicit, according to Rovsing, the typical pain at McBurney's point in case of appendicitis, but not in other abdominal affections. It was never found unless there was some affection of the cecum or appendix.

Diagnostic significance of pain produced by percussion of the abdomen with the rubber-tipped hammer is emphasized. In gastric ulcer of the posterior wall, deep palpation causes no pain, but percussion will reveal it plainly. In appendicitis it will definitely localize the point of tenderness. Involuntary muscular contractions confirm the patient's subjective sensations. The blows of the hammer should be at first light, then stronger, to discover deep painfulness. In gastric ulcer the area of pain is oftenest in the linea alba. In cholecystitis and duodenal ulcer the areas are found near by, on the right parasternal line, the former directly beneath the costal arch, the latter 3 to 5 cm. below it. Guido Izar (*Polí-clínico, Pract. Sect.*, Nov. 14 1921).

Pain is never an absolute indication of the extent of disease. Excessive pain

may be due to kinking of the appendix with complete blocking off of part of its lumen. Its severity also varies according to whether the patient is hyper- or hyposensitive. Peritoneal pain sometimes overshadows the pain in the right iliac fossa caused by tension in the appendix. In rapidly progressive cases bacteria leave the appendix without any macroscopic perforation. Even greater variations occur in the leukocyte count than in the pain. I. S. Raydin (*Internat. Clin.*, June, 1924).

Illoway has noted that invariably (often verified by a subsequent operation), only when appendicitis is present, flexion of the thigh on the trunk causes a feeling of pain or a sensation of soreness deep down and even when this is not so marked the rapid extension causes accentuation of it.

This pain, which is augmented by pressure, deep abdominal respiration, and movements of the right thigh, may be absent or have entirely disappeared after suppuration or gangrene of the appendix has occurred.

Tenderness over the right sympathetic lumbar ganglion ( $1\frac{1}{2}$  inches from the navel on a line with McBurney's point) is a diagnostic sign in appendicitis in addition to the well-known McBurney's point, according to our associate editor, R. T. Morris. In the early stages of an acute infective process of the appendix the right lumbar ganglia are tender and the left lumbar ganglia are not tender. (The left lumbar ganglia may be described for diagnostic purposes as lying an inch and a half to the left of the navel.) Under these circumstances, the point here described is of secondary importance, while McBurney's point is of prime consequence: (a) When an acute inflammatory process of the appendix has subsided, leaving a mucous inclusion or scar-tissue, there may be no tenderness on pressure at McBurney's point, but there is tenderness at the point here described, and no tenderness at the point of the left lumbar ganglia. (b) When the appendix is undergoing a nor-

mal involution process, with replacement of its lymphoid coats by connective tissue, digestive disturbances and various local neuralgias may be due to nerve filaments entrapped in the new connective tissue. There may be no tenderness at McBurney's point, but there is persistent tenderness at the point here described. There is no tenderness at the point of the left lumbar ganglion. When the appendix is congested without the presence of infection, as in many cases of loose kidney, there may be little or no tenderness at McBurney's point, but there is persistent tenderness at the point here described. There is no tenderness at the point of the left lumbar ganglia. Under these conditions, the point here described is of primary importance, while McBurney's point is of secondary or no significance. It will be found useful in differentiating between appendiceal and pelvic irritations. If it is alone tender, it means appendix trouble. If both right and left lumbar ganglia points are tender, it signifies pelvic disorder. If neither of these points is tender, the abdominal irritation must be looked for somewhere higher up than the pelvis or the appendix. It should be kept in mind that McBurney's point relates particularly to acute appendicitis and Morris's point to chronic appendicitis. EDITORS.

To ascertain when the appendix is inflamed, the writer places the patient on his left side, with both anterior superior spines of the ilia perpendicular to the plane of the bed. He then applies pressure to the right side, 3 fingerbreadths inside of and a little below the right spine. This induces sharp pain if the appendix is inflamed and swollen, as it drops down and pulls on the mesentery, which is usually hypersensitive. Rosenstein (*Zentralb. f. Chir.*, June 26, 1920).

Oversensitiveness of the skin over the diseased area may also be present and persist until convalescence begins. It depends upon tension with the appendix. It may be absent in attacks after the first, if the first attack was of sufficient severity to destroy nerve-tissue in the wall of the appendix.

A skin sign considered by the writer of great value in the diagnosis of acute appendicitis consists in comparison of the slight discomfort caused by a vigorous twisting pinch of non-involved skin with the severe pain resulting from the same procedure when carried out within a certain triangle of skin in appendicitis. A line from the umbilicus to the highest point on the right iliac crest forms the upper side of this triangle; a line from this point to the right pubic spine forms its lower side, and a line from the right pubic spine to the umbilicus closes the triangle. Cases in which the maximal intensity of the sign is outside of the triangle, or the sign extends definitely beyond its boundaries, are considered negative for appendicitis. A positive sign above the triangle suggests cholecystitis, etc., while below its inferior line the sign suggests renal colic, etc. In 75 cases of clinical acute appendicitis the sign was positive in 54, all of which were found to have acute appendicitis. Of the 21 negative cases, 11 had gangrenous or perforative appendicitis and 10, other diseases. E. M. Livingston (*Arch. of Surg.*, July, 1923).

Epigastric pain, of a reflex character, has also been observed. If adhesion to the bladder has occurred, pain in the vulva may be caused.

Pain in the cecum is a very common condition in patients with affections of the alimentary tract and is often mistaken for appendicitis. To palpate the cecum, the radial border of the right hand in forced pronation, with the fingers directed toward the pubes, is used to exert deep pressure in the right iliac fossa. In doing so, to and fro movements from the inner margin of the cecum outward are executed, the thumb resting for support against the outer portion of the iliac crest. Repetition of the procedure at different levels permits of ascertaining the situation, margins, shape, and consistency of the cecum. Among 123 patients the cecum was palpable

in 54 and tender in 40. Among the remaining 69, 22 complained of marked pain, radiating toward the sigmoid or epigastrium, upon pressure over the cecum. The cecum was thus abnormal in 66 cases, or 63 per cent.; according to Glénard the normal cecum is neither tender nor definitely palpable. A relationship seems to exist between cecal tenderness and such liver affections as hepatoptosis, hepatic enlargement, gall-bladder pain in the absence of actual attacks of colic, cirrhosis, etc. Of 50 patients with definite hepatic disease, 32 had a palpable or tender cecum. Of 108 patients with gastric disorders causing objective signs, 72 had an abnormal cecum. L. Pron (*Bull. de l'Acad. de Méd.*, Feb. 5, 1918).

Constipation is present in the majority of cases. Nausea and vomiting are also present in most instances, but they do not always furnish information as to the seriousness of the case. They may occur coincidentally with the attack or shortly after. Nausea and vomiting are purely reflex, but are very constant symptoms, being due to irritation having its origin in the appendix. They may cease when the stomach is emptied of its contents, but may return when other causes are brought into play, as, for instance, peritonitis due to perforation.

In about 1 per cent. of all cases one may expect to find the appendix densely adherent to the terminal ileum. The writers regard the following symptom-complex as almost pathognomonic of this condition: Recurring attacks of pain in the lower right quadrant, either accompanied or followed by diarrhea; a tendency to diarrhea on the least provocation. (The diseased appendix adherent to the terminal ileum has a tendency to rush peristalsis and to render the ileocecal valve incompetent, with resulting diarrhea.) There is usually a history of one or more disabling illnesses due to gastric upset, ab-

dominal pain and some fever, followed by an interval of sensitiveness in the right iliac fossa and an associated mild dyspepsia. There are usually present foci of infection, oftenest in the tonsils, occasionally in the teeth or elsewhere. Appendectomy and restoration of the ileum to its normal position results in cure. The foci of infection should be removed either at the same time as the appendectomy, or soon after. In this condition the appendiceal disease probably starts in the walls of the appendix; the serosa becomes involved early, but the mucosa only late, or not at all. Sheldon and Heller (*Jour. Mo. State Med. Assoc.*, May, 1923).

The tongue is usually coated. The respiration is not materially influenced unless peritonitis develops, when it becomes costal.

The pulse and temperature are apt to vary considerably in different cases and do not bear a definite or constant relation to the severity of the disease, though a sudden rise of temperature, or of the pulse rate, or both, generally indicate extension of the morbid process to the peritoneum. A slow pulse is thought by Kahn to indicate that gangrene of the appendix is present.

A difference between the axillary and rectal temperatures is noteworthy in appendicitis. Normally, the rectal is  $0.6^{\circ}$  C. higher than the axillary temperature, but in appendicitis this difference is greatly increased, even to  $1.4^{\circ}$  C., due to the hyperemia of the pelvic viscera.

A temperature of 99 to  $101^{\circ}$  F. may be considered typical in appendicitis. The first symptom, however, is pain, which is colicky and intermittent at first, reaches its height in from four to ten hours, is referred to the epigastrium or just above the umbilicus, later radiates to the right lower quadrant or in the direction in which the appendix may be pointing, then becomes constant. By the third day,

pain is less or absent, indicating resolution; or it may become severe, indicating a spreading peritonitis. Tenderness exists in every case, beginning with general abdominal sensitiveness, or, if localized, is a sure guide to the site of the trouble. Nausea or vomiting is an important diagnostic feature, but not always present. A sudden drop in temperature may be due to drainage into the cecum with resolution, to perforation, or to gangrene. Septic absorption causes leukocytosis. A stationary white count with increasing percentage of polynuclears points to gangrene. W. Jamieson (*Canad. Med. Assoc. Jour.*, Apr., 1922).

Anorexia and digestive disorders are rarely absent. Diarrhea and constipation may alternate, but the latter is more frequently observed, especially at the onset of the attack. Jaundice is occasionally noted, especially in severe cases. Reichel, among 165 of his cases of appendicitis, noted jaundice in 18; of these, 10 resulted fatally.

New sign of appendicitis, consisting of pain upon pressure on the right phrenic nerve. With the patient's head turned to the left, a fingertip is placed between the 2 sections of the sternocleidomastoid close to the sternoclavicular joint. The head is then turned to the right and light pressure made. A positive result is shown by wincing and the facial expression. Iliescu (*Bull. de l'Acad. de méd.*, Jan. 26, 1926).

Rigidity of the right abdominal wall is generally present, but circumscribed rigidity over the region of the appendix occurs in about one-half of the cases. The degree of rigidity usually corresponds with the intensity of the local inflammation. Tympanites is often present if there be peritoneal inflammation of the adjacent intestinal coils.

Rigidity of the lower half of the right rectus muscle is almost always present, as is tenderness on pressure in this region. Most difficulty is encountered where the obstructed appendix is lying high up in the retrocecal region, but even here some hyperesthesia of the skin above McBurney's point, together with tenderness in the lumbar region posteriorly and a normal urine, incriminate the appendix. The importance of making a diagnosis on the local signs cannot be overemphasized, because in these cases to wait for changes in the temperature or pulse-rate so often means delaying until gross pathological changes have supervened and the danger zone has been entered. Wilkie (*Edinb. Med. Jour.*, Nov., 1920).

The writer makes use of the reflex re-education in abdominal tension after filling of the stomach to relax the abdominal walls during palpation. The patient assumes an easy dorsal position and drinks out of a vessel with a spout, by separate swallowing acts. The head remains recumbent while the fluid is taken in swallows as long as possible without inspiring air. Good results on palpation are thus obtained. Contractions of the abdominal wall due to inflammatory processes do not relax under the procedure. G. Kelling (*Munch. med. Woch.*, Dec. 9, 1921).

If the case be one of simple catarrhal appendicitis, the above symptoms continue two or three days, and the patient gradually recovers.

The differential blood-count and its relation to the total leukocytosis are today the most valuable diagnostic and prognostic aids in acute surgical diseases that are furnished by any of the methods of blood examination. They are of value chiefly in indicating fairly consistently the existence of suppuration or gangrene, as evidenced by an increase of the polynuclear cells disproportionately high as com-

pared to the total leukocytosis. The greater the disproportion, the surer are the findings, and in extreme disproportions the method has proved itself practically infallible. If the leukocytes number more than 14,000, and especially if the polynuclears are more than 70 per cent., an early operation is indicated unless there be strong reasons for not doing so.

An index of the degree of infection is afforded by the percentage of polynuclears, while the general leukocyte count indicates the capacity of the system for resistance to invasion. Gibson's chart method of determining the severity of appendicitis described thus: The total leukocyte count is marked on a vertical line at the left, beginning below at 5000, and the polynuclear percentage on a vertical line at the right, with the notation 70 per cent. opposite the 5000 on the left, 75 per cent. opposite 10,000, etc. The days of the week are represented by 7 intervening columns. Each day the total leukocyte count is recorded along a line running toward the left and the polynuclears on a line running toward the right. If a line is high in the chart and inclined upward from left to right, resistance is poor; if it is low or tends downward, a favorable condition is indicated. A high curve with a downward tendency suggests medical treatment; with an upward tendency, operation. Sarraga (*Bull. Porto Rico Med. Assoc.*, Apr. 30, 1922).

Systematic blood examination affords the best indication as to whether an appendicitis has subsided sufficiently for the safe performance of an interval operation. The leukocyte count, and especially that of the polynuclears, are of prime importance. Absence of polynucleosis is a valuable sign, justifying operation without hesitation. De Martel (*Presse méd.*, Mar. 3, 1926).

Variations from the above course are met with. The disease may come on insidiously, and fever or pain be absent.

Case in which pain and rigidity were absent in an attack of appendicitis terminating in abscess formation. The patient had had fever for one day, but it had disappeared, along with all tenderness, after a dose of castor oil. In view of the typical attack of appendicitis the man had had three months before, appendectomy was performed eight days after the mild disturbance. Evidences of a recent acute inflammation were found, with a small peri-appendicular abscess. Scigliano (*Riforma med.*, Apr. 10, 1922).

Although such an insidious onset is occasionally met with in adults, it is most likely to occur in children. Occasional colicky pains are sometimes the only early signs furnished, these being followed by the typical symptoms.

In children clean cases of appendicitis (those in which it is not necessary to insert a drain) are unusual. In reviewing the case records at the Samaritan Hospital two years ago, the writer found that at least 90 per cent. of patients under 15 had peritonitis, either local or general, and that the mortality was four times greater than in a corresponding number of adult cases. J. O. Bower (*N. Y. Med. Jour.*, Sept. 21, 1918).

The symptoms of appendicitis often are few, irregular and misleading in children. Pain is more frequent and severe than is generally believed. All abdominal pain in children should be looked upon with suspicion. Roy Roberson (*Med. Rec.*, Jan. 8, 1921).

Slight appendicular lesions may be accompanied by alarming symptoms in hysterical patients, or in those mentally and physically below par. Renal and cystic phenomena, including renal colic and painful micturition with tenesmus, may also occur.

Following genitourinary symptoms noted in acute appendicitis: Frequency of, and pain during, micturition, or retention or difficulty in urinating; tenderness on pressure in either or both testicles and retraction of the latter;



tenderness in the erector-costal angle. Confusion may occur with acute pyelitis, but while in the latter the abdominal muscles are lax and there is pus or bacteria in the urine, the urine is free of these in appendicitis, while the abdominal muscles are apt to be rigid. V. Z. Cope (Proc. Roy. Soc. of Med., Urol. Sect., Nov., 1921).

Case in which an attack of appendicitis was diagnosed as stone in the ureter. There were pain in the right side, frequent passage of scanty amounts of urine, severe paroxysmal pain in the right testicle and head of the penis, cold clammy perspiration, no spasm of the recti, no palpable masses, slight tenderness in right kidney region, scarcely perceptible tenderness on deep pressure in the lower right quadrant, temperature subnormal, leukocytes 9800, urine loaded with red cells. Four days later the patient felt well, but six days after this was readmitted with pain in the right side, frequent vomiting attacks, tenderness at McBurney's point, slight spasm of the right rectus, fever, and leukocytes 16,200. The appendix was found adherent in the right lumbar region, lateral to the ascending colon, with its tip gangrenous. Apparently a diseased appendix may cause hematuria by direct irritation of the kidney or ureter. A. P. C. Ashhurst and L. G. Woodson, Jr. (Jour. Amer. Med. Assoc., Dec. 23, 1922).

Chills sometimes occur, but they usually coincide with gangrene of the appendix or with the formation of a local or metastatic abscess. When an abscess or a fibrinous exudate forms about the appendix, it may usually be detected by palpation, being fixed and smooth, surrounded by an area of tympanites. Rarely it may fluctuate, especially when large. Any considerable pressure should be avoided, since it might cause rupture of the abscess. Rigidity usually disappears when such an abscess or the infected focus becomes encapsulated.

Progress toward perforation either into the general peritoneal cavity or into a cavity formed by adhesions is probable when, on the third day, or even earlier, after the onset of the symptoms, there is a localized superficial edema, indicating deep suppuration, and when a doughy mass is felt at the seat of pain, which mass gradually assumes shape to the touch, unless distended intestinal coils, shown by local tympanites, or the tension of the abdominal walls, make its detection impossible. Perforation is also often indicated by a cessation of pain and an increase in the tension and frequency of the pulse rate.

If suppuration is present and perforation occurs on the fourth or fifth day, *i.e.*, after the adhesions have formed, the symptoms do not, as a rule, vary from those enumerated. When, however, they do not assume a graver form during the first four days, the presence of protective adhesions is likely. The presence of general rigidity over the whole lower abdomen, even with little rise of temperature and slight increase in the pulse rate, indicates perforation with secondary abscess in the pelvis.

When the symptoms are marked and a tumor cannot be felt, perforation has probably occurred before the adhesions were sufficiently perfect to protect the peritoneal cavity.

If perforation has occurred early, *i.e.*, while the adhesions were still imperfect, there is usually a chill and vomiting; shock, more or less profound; diffuse, marked pain, instead of the localized pain; acceleration of the pulse; an increase of temperature of 2° or 3° F.; scanty and dark urine, showing high specific gravity.

Perforation is also accompanied by distention of the abdomen, and symp-

toms of grave diffuse peritonitis appear, followed by collapse. Dullness, especially in the right iliac fossa, affords an early clue to the presence of pus.

In *fulminating appendicitis*, termed such owing to the rapidity with which the disease progresses, the peritoneum may be involved within a few hours. Again, in the midst of what apparently is a mild case, abscess, gangrene, and perforation may suddenly appear with all their disastrous sequelæ. This indicates the necessity of giving the greatest attention even to apparently benign cases.

When appendicitis occurs during pregnancy the attack is usually sudden and begins with abdominal pain, which gradually becomes localized; this is followed by the typical symptoms. This condition must be carefully differentiated from tubal pregnancy. The prognosis is grave. The chances of abortion following operation are not great, provided a speedy operation is done. In the last half of the pregnancy the condition is much worse and operation is more difficult.

Out of 10 women who had had, prior to conception, repeated attacks of appendicitis, 6 had recurrences in their first pregnancies. Four were operated early in the attacks, without any post-operative disturbances. In the others drainage was required. Perforation of the appendix and peritonitis during pregnancy are severe. If an abscess becomes walled off, it is apt to rupture in labor. In operating between the first and fifth months a right rectus incision is suggested, to inspect the tubes. After the fifth month a higher incision and liberal drainage are advised. If abortion is inevitable the uterus should be emptied. W. L. Crosthwait (Texas Med. News, xxv, 337, 1916).

Pregnancy may be confused with acute appendicitis. A fibroid or sub-

peritoneal tumor, as the uterus increases in size, may be squeezed between the developing uterus and the bony pelvis or abdominal wall, and the resulting pressure cause it to be pressed into the uterine wall like a cork in a bottle until its circulation is cut off and inflammation set up. The pain, tenderness and muscular rigidity frequently lead to the diagnosis of appendicitis. He has seen 3 such patients, 2 of whom were subjected to operation for supposed appendicitis. In acute appendicitis complicating pregnancy, the cecum generally is fixed, the gravid uterus lies in front of it, and the pain may be aggravated by making pressure over the uterus or by pushing behind the uterus. In a fibroid causing the condition the pressure and pain are more anterior to the position of the appendix. W. W. Montgomery (N. Y. Med. Jour., Nov. 13, 1921).

During examination gentle manipulation is necessary, lest an abscess be present and the adhesions be delicate and unable to stand the traction or pressure.

The location, direction, and extent of the appendix have an important bearing on the clinical history of appendicitis, considering the variations of the appendix in length, direction, and location and the varying site of the cecum.

Description of an ectopic, subhepatic form of appendicitis believed to occur in about 2 per cent. of all cases, 10 such cases having been met with in a series of 500. Unusual mobility of the cecum and a high position of the appendix are the underlying features in these cases, which sometimes simulate hepatic colic. To the usual symptoms of acute appendicitis may be added biliary symptoms such as slight jaundice. The condition is distinguished from an actual pericholecystitis by a more lateral and slightly lower location of the exudative masses; by the greater extent of the latter and their uneven surface, and by the facts that they may at times be displaced still lower,

that they are independent of the movements of the lower border of the liver, and that a zone of tympany often separates them from the liver dullness. In gallstone colic the pain is sharper and more intermittent than in appendicitis. The prognosis in this type of case is generally favorable. In operating, a rather high pararectal incision should be made. O. Cignozzi (*Riforma med.*, Feb. 13, 1922).

Auscultation of the lungs and heart sometimes affords information.

Examination through the rectum is of value in determining the presence of pus in advanced cases, especially in children. In the earlier stages this procedure is not very helpful.

High palpation of the right iliac fossa by rectum elicits tenderness and pain in the McBurney region in children. The examining finger must be introduced quite painlessly. This can always be done if patience is exercised. The valuable diagnostic point is that the patient complains of no discomfort until the finger reaches the right iliac fossa, when a sharp pain in the vicinity of McBurney's point is elicited. F. L. Wachenheim (*Arch. Pediat.*, xxxiii, 197, 1916).

Examination of the urine may assist in the location of the inflammatory process and in determining the activity of metabolic processes. Glycosuria has also been observed.

**Children** often suffer from appendicitis, the gastrointestinal disorders to which they are subject being not infrequently related with a diseased appendix. The symptoms do not differ essentially from those in adults, but are apt to develop more rapidly.

In diagnosing appendicitis in a small child, the writer places the patient on the floor and observes it as it runs to its mother. The psoas symptom, often absent in bed, thus becomes readily observable. Wolf (*Munch. med. Woch.*, Feb. 20, 1925).

Following is a summary of data from F. Beckman's (*Ann. of Surg.*, Apr., 1924) analysis of 145 operated acute cases in children:

	NON-PERFORATING CASES.	SPREADING PERITONITIS.	ABSCESS CASES.
Total number.....	48	44	53
Mean temperature.....	101.3°	102.1°	101.5°
Mean pulse rate.....	113	127	116
Mean respiratory rate.....	25	32	32
Pulse-respiration ratio.....	4.5	4	4.1
Vomiting (per cent.).....	85	97.7	83
Abdominal tenderness not general (per cent.).....	87.5	22.7	83
Abdominal mass (per cent.).....	0	4.5	34
Mortality.....	0	18.2	5.7

To facilitate diagnosis in doubtful cases in infants and young children that cry on examination, Crile gives the child "twilight" ether anesthesia. Under deep pressure there is a distinct muscle reflex on the right side when appendicitis is present. If pressure is made when the anesthesia has faded to the subconscious state, there is a significant pain response.—EDITORS.

In a study of 313 cases of appendicitis in children 14 years of age or younger, comprising 175 boys and 138 girls, the symptoms in the acute cases (87 per cent.) varied considerably. Besides cramp-like abdominal pain, vomiting, abdominal tenderness becoming localized in the right iliac fossa, and fever, many had a chill at the onset, 80 per cent. showed sweating, and many had urinary symptoms, cough, constipation, diarrhea, and abdominal distention with or without tumor mass. The lesser attacks are apt to be masked as stomach-aches until stirred up by an overdose of cathartic, severe constipation or diarrhea. Because of the slight development of the omentum in children, the omentum cannot be depended upon for much assistance in walling off the infective process. General peritonitis was present on admission in 6 per cent., intra-abdominal abscess in 26.8 per cent., ruptured appendix in 27.7 per cent., and gangrenous appendix, either ruptured or floating in pus, in 23.3 per cent. The leukocyte count

gave little help, being high in unruptured as well as ruptured cases; the former showed a low count, however, 9 times as often as the latter. In abscess cases, the writer favors drainage as soon as the condition is recognized. Pain is of little diagnostic or prognostic value; in many cases with an overwhelming infection there is little pain. After the appendix ruptures, there is frequently, as in adults, a subsidence of the symptoms which may be misleading. When the child will not permit palpation the abscess may be felt through the rectum. There were 19 deaths, a mortality of 6 per cent. All of these had had catharsis before admission. Of the whole series, 95 per cent. had had catharsis. K. Speed (*Amer. Jour. of Surg.*, May, 1923).

The diagnosis of appendicitis in infants and small children may be facilitated by the induction of scopolamine-morphine anesthesia, when pressure on the appendix will cause a muscle spasm. W. E. Lower and T. E. Jones (*Jour. Amer. Med. Assoc.*, Aug. 25, 1923).

In children, because of mobile cecum and long appendix, the inflammation may start away from McBurney's point, and may be so deeply placed in the pelvis that suprapubic pressure may not cause pain. Rectal examination is indicated. When the inflamed appendix is in the pelvis, pain on micturition or voluntary retention of urine, or constipation due to unwillingness to allow a movement, or possibly a diarrhea due to irritation of the rectum, may be among the symptoms noted. In cases of pelvic appendicitis which go on to abscess formation, it is not at all uncommon for the abscess to appear on the left side; when the abscess has filled the pelvis the path of least resistance may be up along the rectum and sigmoid. The appendix is often placed just inside the mesocecum, behind the cecum and the loops of the ileum. The tenderness under these circumstances is often masked by the air cushion of the overlying bowel.

In thoracic disorders simulating appendicitis the examiner's fingers may, if moved very slowly and carefully, palpate the abdomen freely, the immobility of the hand causing a relaxation of the muscular spasm. In appendicitis spasm increases as the muscles attempt to prevent the fingers from pressing on a tender spot. J. S. Stone (*Boston Med. and Surg. Jour.*, Aug. 30, 1923).

Stress laid on pneumonia as a possible factor in diagnosis when symptoms of appendicitis are present in children. In appendicitis the rise in temperature is gradual and seldom attains 103 or 104°. In a fulminating attack the temperature may be no more than 99.5 or 100. The leukocyte count, according to Harris, is usually moderate in appendicitis, seldom being over 20,000, and more often nearer 12,000 or 15,000. In a series of pneumonia cases, 90 per cent. gave a leukocyte count of more than 20,000, and only 9.8 per cent. were below 15,000. A leukocyte count near or over 20,000 should make one think strongly of pneumonia. The value of pain, tenderness and rigidity in diagnosis depends on the age, intelligence and character of the child. Some little children, however, give surprising assistance by their bright responses, localization of pain, and reaction to pressure over the affected area. The X-ray is of value, and may disclose a small affected area of the lung or a central pneumonia giving few or no clinical signs. One of the cases reported by the writer is that of a boy aged 4, complaining of pain in the abdomen, headache, vomiting, and frequent urination. He lay with both hands pressed over the abdomen, and alternately groaned and cried with pain. Lungs negative. Abdomen slightly distended and tympanitic. Degree of rigidity and of tenderness in the right lower quadrant hard to determine. Temperature, 102°, leukocyte count, 36,000. Operation was advised because of the chance of overlooking a fulminant appendix. But soon the temperature crept up to 103°

and later to 105.4° by rectum; the thought of operating was thereupon abandoned. The leukocytes rose to 51,000. A mild cough had developed, but no clinical signs of pneumonia were present. On the third day the temperature dropped to 99° and the patient recovered uneventfully. P. A. White (Jour. Amer. Med. Assoc., Mar. 1, 1924).

**Bastedo's sign** has been found useful by some observers and valueless by others. It consists, after carefully cleansing the bowel, in distending it with air through a rectal tube. If the appendix is diseased pain is complained of at McBurney's point.

**DIAGNOSIS AND COMPLICATIONS.**—Although the three cardinal symptoms: pain, tenderness, and rigidity, render the diagnosis of acute appendicitis comparatively easy, the fact remains that many conditions simulate it and may, therefore, lead to a mistake. Yet, it should be remembered that several of these disorders may actually be present as complications, as several examples submitted below will show.

Quite prominent in this connection, of course, are disorders of the gastrointestinal canal: intestinal obstruction, volvulus, perforation or foreign body, inflammation of Meckel's diverticulum, and acute infections of the gall-bladder. The fact that some of the symptoms of the latter and of hepatic disorders, especially jaundice, as we have seen, may occur as complications of appendicitis serves further to complicate the situation. Several observers have concluded that cirrhosis of the liver may be one of the complications of appendicitis.

Case of persistent patent Meckel's diverticulum simulating appendicitis. Operation showed the presence of an abscess. The localized tumidity and

tenderness were located rather higher and nearer the middle line than usual. Glover (Lancet, Mar. 3, 1917).

In cases with afebrile abdominal pain, the knee-jerks should be tested, to rule out the gastric crises of tabes. Nervous individuals often work themselves up into a mental state closely resembling appendicitis. Bloch (Internat. Jour. of Surg., Mar., 1922).

The following features are diagnostically serviceable in children under 5 years: The appendix being relatively long in children, when there is peritonitis, even if localized, the pain may be low down in the pelvis, high up in the abdomen or in the back, or even on the left side. In a very young child, pain may be inferred from constant crying and restlessness, and disturbed sleep. (Children with pneumonia or other fevers usually sleep for long stretches). The pain is nearly constant, but with localized suppuration may be increased by defecation or urination. Absence of pain on sitting up argues against appendicitis. The child may limp. Fever is often not above 101° F. The same is true of the leukocytosis. Vomiting at the start is seldom absent, and may continue throughout. Constipation is more frequent than diarrhea. Tenderness is rarely wanting, and usually extreme, though in appendicitis due to intestinal parasites it may be insignificant. J. Howland (Jour. Amer. Med. Assoc., Sept. 27, 1924).

Gastric disorders may, in fact, be traced directly to a chronically inflamed appendix, and as such to acute exacerbations of appendicitis. Gastric ulcer—with marked gastric pain after taking food; eructations, hyperchlorhydria, etc.; nausea, vomiting and even hematemesis, and blood in the stools; melena—has also been diagnosed where the causative lesion, as demonstrated by the normal condition of the stomach and the result of removal of the diseased appendix, lay clearly in the latter.

After studying 1400 cases, including 300 designated as pseudoappendicitis, the writer contends that faulty differential diagnosis very often is due to perimetritis, also pyelitis or pyelonephritis, renal colic, enterocolitis, and acute inflammation of the cecum. He urges that it is not sufficient to determine pain at McBurney's point, spastic contractions of isolated portions of the intestine, etc. In many cases, spastic contractions will disappear during narcosis and before the beginning of the operation. Intestinal spasms are frequent and often mistaken for chronic appendicitis. Such neuroses require no operation, while **atropin**, given 3 weeks, is efficient: 0.001 to 0.0015 Gm. ( $\frac{1}{16}$  to  $\frac{1}{15}$  grain) of atropin sulphate in pills each day. In severe cases, a 1:1000 solution of atropin sulphate (for 5 days, 3 times 4 drops; next 5 days, 3 times 8 drops; then 12 drops 3 times daily, and back to 4 drops). E. Lick (Mittheil. a. d. Grenzgeb. d. Med. u. Chir., xxxii, No. 2, 1920).

Floating kidney with torsion of the ureters, nephritis with hematuria, renal or hepatic colic, ovaritis, extra-uterine pregnancy, ovarian cyst with twisted pedicle, pelvic cellulitis, dysmenorrhea, inflamed undescended testicle, epididymitis and hernia, incipient or strangulated, have all caused confusion.

The writer operated for combined chronic appendicitis and hernia in 53 children. When a child has pains from an inguinal hernia, or undescended testicle, appendicitis should always be suspected. One may preferably operate separately on the hernia and the appendix, except in small children not in an acute stage. Veau (Bull. de la Soc. de Pédiat., May 5, 1914).

Retraction of the testicle is occasionally observed in appendicitis and is due to irritation of the genitocrural nerve. Pain in one or both testicles may occur in acute appendicitis, generally accompanying perforation. It may precede the onset of

the abdominal pain by an hour or two. It may well be a referred pain, the two structures being supplied from the same segment. When a pelvic abscess has formed, irritation of the vas deferens and seminal vesicles may result. Z. Cope (Brit. Jour. of Surg., Oct., 1921).

Hematuria in appendicitis may be produced either through the circulation, through an embolic infarct, by general infection (glomerulonephritis), by direct propagation from neighboring organs (colon bacillus nephritis), by kinking of the ureter as a result of adhesions, and reflexly through the sympathetic nerve. In a case reported by the writer, the patient had had pains in the right hypochondrium for four years. There were many evidences of renal disease, including three apparent shadows of stones. The kidney was removed, but showed only some small cysts and fibrotic areas. Later a tender tumor, with fever, developed in the gall-bladder region. At operation a long inflamed appendix was found coursing back of the normal gall-bladder up to the right lobe of the liver. Its removal proved curative. A. von der Becke (Zeitschr. f. Urol., No. 2, 1922).

Case in which an exudate in acute appendicitis brought about hematuria by exerting pressure on the right ureter. M. Ascoli (Policlin., Mar. 16, 1925).

A psoas abscess, fecal impaction in the right iliac region, tumors, lymphadenitis, aneurism in this area, tabetic crises in the abdomen, lead colic, pneumonia, pulmonary abscess, and pleurisy have all proven misleading. The two latter disorders may, in fact, be associated with appendicitis, *i.e.*, appear as one of its complications. According to Sonnenberg, the greater number of cases in which there are lung complications originate from emboli; Gussenbauer has had a similar experience. In the hospital at Moabit, out of 740 cases 28 had some lung complications, and,

of these, 14 were cases of thrombosis; in the private clinic, out of 260 cases, 19 had some lung complication.

The writer observed several cases in which râles, congestion in the apices, and other symptoms of pulmonary tuberculosis fluctuated with exacerbations of chronic appendicitis, and disappeared completely after appendicectomy. In three of the cases, consultants did not accept his diagnosis until two of the apparently doomed patients regained their health after the appendicectomy. Schoull (Paris méd., Oct. 12, 1918).

Thrombosis in the veins of the jejunum or other neighboring structures may not only give rise to acute symptoms recalling those of appendicitis, but it may also occur as a complication of the latter. Phlebitis, edema, obstruction of the portal system and of the mesenteric, omental, gastric, iliac, and other veins have also been traced to this cause.

From the standpoint of differential diagnosis the *main* disorders which tend to cause confusion and the symptoms which help to identify them are the following:—

**Intestinal Obstruction.**—In this disorder the rise of temperature occurs late. Stercoraceous vomiting is observed in serious cases. Volvulus generally presents itself in children. There is more distention and no abdominal rigidity. The pulse and temperature are normal in the early stages. Intestinal obstruction may, however, attend or follow appendicitis.

Subacute intestinal obstruction sometimes follows acute appendicitis, either because of circumscribed intestinal paralysis in beginning peritonitis, compression of the bowel by an abscess, or adhesion of bowel loops to the abscess wall. The symptoms of obstruction usually begin after six or seven days of improvement from

the acute attack. The condition is distinguished from progressive peritonitis by the relative softness of the abdominal wall, increased peristalsis and comparatively slight general illness. The treatment in the abscess cases is appendectomy and drainage. A. Jirasek (Casopis lek. cesk., Jan. 21, 1922).

**Tuberculous Typhlitis.**—Slow asthenic course, diarrhea, and a higher temperature usually distinguish this disease. The appendix itself may also be the seat of the tuberculous process.

The writer observed 12 cases of acute tuberculous inflammation of the ileocolic glands, with the symptoms those of acute appendicitis. In no case was a palpable tumor present. In some there had been a history of one or more previous attacks of appendicitis. The simulation is so close that a differential diagnosis is almost impossible. The appendix was usually removed, but no tubercle bacilli could be found in it. The infected glands were dissected out. The prognosis is good, only 1 case developing a tuberculous taint. Homer Gage (Boston Med. and Surg. Jour., Aug. 26, 1915).

About 05 per cent. of all appendices removed surgically are tuberculous. The writer had one case in 179 appendices examined. There is an afternoon temperature, progressive weight loss, evening sweats and pain and tenderness in the right lower quadrant. The prognosis is unfavorable except in the very rare primary forms of the disease, but best in the hyperplastic form. J. R. Scott (Annals of Surg., Dec., 1917).

**Tumors.**—In cancer, the neoplasm which occurs most frequently in the intestines, the subject is usually beyond his 40th year. The progress is slower and the temperature seldom much above normal. Cancer of the appendix, or involvement of the latter, have also been observed.

The total number of cases of carcinoma of the appendix in the litera-

ture, including 40 cases discovered among 8039 appendices examined microscopically at the Mayo Clinic, and 24 treated there subsequently, is given by the author as 317. Operation resulted in cure of the malignant condition in all of the 37 cases (out of 64) traced. It thus offers the most favorable prognosis of all forms of malignancy of the gastrointestinal tract. A pre-operative diagnosis of the condition is impossible. Obliterated appendices should be examined carefully for signs of malignancy. Of the 64 specimens, but 1 was diagnosed as colloid carcinoma; the rest were placed in the spheroidal group. The latter type rarely invades the cecum or metastasizes to the abdominal glands. Out of 24 cases the growth occurred at the tip of the appendix in 21, at the base in 2, and in the middle in 1. The tumor *in situ* grossly suggests concretions within the lumen. When preserved in formalin it is of an orange color. Fifty per cent. of the patients gave a history of previous trouble. There were twice as many women as men. A. S. Jackson (Arch. of Surg., Mar., 1923).

**Typhoid Fever.**—Perforation occurs late in this disease, while the temperature, the petechiae, and other characteristics readily serve to distinguish it. In case of doubt the blood should always be examined for the Widal reaction.

**Pneumonia and Pleurisy.**—In some cases the symptoms closely resemble those of pneumonia or pleurisy. An examination of the lungs will clear up this point. In the former a sudden and persistent rise of temperature may occur.

In the differentiation from early pneumonia, the author regards spasm of the external oblique in its uppermost fibers as indicating chest involvement, whereas spasm of the lower fibers suggests appendicitis. A temperature of 102° F. or over is strong evidence against appendicitis

in the first 24 hours. Anything resembling a chill favors chest infection, as does also a full, bounding pulse or a leukocytosis of 25,000 or over. The abdominal respiratory movements are more impaired by peritoneal infection than by pleuropulmonary irritation. In pneumonia blood cultures are positive early. R. St. L. Brockman (Pract., Aug., 1924).

**Disorders of the genitourinary organs,** uterus, adnexa, and pelvic cellular tissue, especially salpingitis, are conditions which may cause confusion. Examination of the genitourinary organs sometimes establishes the differential diagnosis, but occasionally complications occur which render it difficult. X-ray examination is of great aid in this connection.

In making an X-ray diagnosis between ureteral calculi and calculi of the appendix, one should remember that ureteral calculi are situated more internally. An error is possible only when the appendix lies over the psoas and hanging over the brim of the pelvis, and is much elongated. Impacted gall-stones appear at a higher level. G. Vilvandre (Arch. of Radiol. and Electrotherapy, July, 1916).

Appendicitis in the female can be mistaken for pyosalpinx, ovarian abscess, suppurating ovarian cyst, torsion of the pedicle of an ovarian cyst, ectopic gestation, abortion and dysmenorrhea. Bimanual or recto-abdominal examination should be part of the physical examination of every female patient beyond the age of puberty. Acute pelvic inflammation is usually preceded by vaginal discharge and dysmenorrhea, and appendicitis, by digestive disturbances or previous attacks of pain on the right side. In pyosalpinx the pain is more constant and less severe and is situated lower in the pelvis, the tenderness being frequently most acute over Poupert's ligament. In the other conditions a carefully taken history and physical examination usually make the diagno-



sis clear. F. C. Hammond (N. Y. Med. Jour., June 5, 1920).

To distinguish appendicitis from adnexitis, the writer adopts the following procedure: The patient, sitting erect in bed, is required to raise her extended right leg, with some assistance from the observer. To keep the trunk upright, an assistant meanwhile makes pressure against the back. In appendicitis this results in sharp pain at the junction of the middle and right thirds of a line joining the spines of the ilia, the cecum being compressed between the psoas muscle and abdominal parietes. In adnexitis, the pain produced is somewhat lower and more to the right. The test was uniformly useful in 150 cases. Sattler (Deut. Zeit. f. Chir., Oct., 1924).

In cases in which there is doubt as between appendicitis and acute salpingitis, treatment as for the former should be applied. Out of 24 such cases seen by the writer, 21 turned out to have appendicitis alone, while 3 had salpingitis plus a more or less marked appendix involvement. In the 21 purely appendix cases, many had leukorrhea; menorrhagia was present in 8 and urethritis in 3, while 7 had tenderness above and to the left of the symphysis. Ten Berge (Nederl. Tijds. v. Gen., Jan. 16, 1926).

By placing the patient on her left side with the shoulders low and the legs drawn up, it is much more easy to detect the position and condition of the appendix, and also to differentiate it from the uterine adnexa, than by palpation of the patient lying on her back. Even when no great intestinal distention is present, the depth at which the appendix might lie is greater, and the tension of the abdominal walls is likely to be more marked in the dorsal position than when this lateral method is employed, if no intestinal adhesions are present.

In appendicitis the pains are more violent, but more strictly localized,

and radiating pains are absent. In catarrhal salpingitis, especially if the ovaries share in the inflammation of the tubes, the pains radiate toward the thigh; the alarming symptoms also show a noticeable remission toward the third or fourth day.

In an acute progressive case of appendicitis, the abdomen is so rigid that deep palpation is difficult and dangerous. A rigid abdomen, according to Robert T. Morris, is the principal differential sign between acute appendicitis and salpingitis.

In appendicitis the boundaries of the area of sensitiveness to percussion and hyperesthesia are a few finger-breadths from the midline and the groin. In adnexal disease the area reaches to the midline and the groin. In appendicitis the area is more nearly round, while in adnexal disease it is often a transverse oval and runs upward in a more nearly straight line. In acute disease of the adnexa it is almost always bilateral. The dorso-linear hyperesthesia of the skin, most marked between the long muscles of the back and the scapular line, is often completely lacking in appendicitis, but is rarely absent in acute disease of the adnexa. In the latter there are also bilateral hypersensitive areas of skin running straight or obliquely downward from the level of the first lumbar vertebra to the first third of the sacrum. W. Mayer and Uhlmann (Med. Klinik, Feb. 13, 1921).

The cecum reaches into the small pelvis in 30 per cent. of women, and is in contact with the adnexa. The lymph-vessels between the appendix and adnexa of the right side communicate in 22 per cent. The appendiculoovarian ligament is involved, so that an inflammatory process may extend from one to the other. Sudden abdominal pain in a virgin suggests appendiceal involvement, while previous genital trouble indicates adnexal disease. W. Liepmann (Deut. med. Woch., Feb. 16, 23, Mar. 2, 10, 1922).

Case of a man who suddenly developed pain over the right groin and bladder with frequent micturition and scalding. By the third day he had a well developed right epididymitis. No gonococci were found in the urethral discharge. No abdominal symptoms. Three weeks later he developed a left epididymitis, without urethral discharge, and on the seventh day, pain in the right lower quadrant. There was deep tenderness and a mass rising upward toward the right side was felt per rectum. At operation the pelvis was found filled with matted coils and the tip of the appendix perforated and adherent to the base of the bladder. In the culdesac a small abscess was found and opened. Dansey (*Med. Jour. of Australia*, Jan. 12, 1924).

According to Deaver, **movable kidney** is to be differentiated as follows: In appendicitis there is more apt to be fever and increased pulse rate, the rigidity of the abdominal wall does not involve such a large area, there is a circumscribed and acutely tender point, the tenderness is more superficial, and there is an absence of a movable tumor which readily slips from between the examiner's fingers.

Infectious catarrhal inflammation of the **bile-ducts** and ulceration of these ducts may occasionally simulate appendicitis. Biliary colic is to be differentiated by jaundice, absence of fever, peculiar color of the stools, finding of gall-stones in the passage, and by the more severe and continuous pain, radiating usually from the chest margin to the umbilicus. The typical pain in the right shoulder-blade is an important diagnostic sign of gall-bladder disease.

Aside from appendicitis there are 3 common right-sided abdominal conditions which may be present when there is pain in the right iliac region: Acute gall-bladder or kidney disease, and perforations of the gastro-intes-

tinal tract. Murphy's signs are of great help in the differentiation. To test for gall-bladder disease by the hammer-stroke percussion method, the observer sits on the right side of the recumbent patient, flexes his second left finger to a right angle, and sinks it underneath the 9th costal cartilage. As the patient takes a deep inspiration, the gall-bladder is forced down and the flexed finger then struck with the ulnar border of the right hand. If the gall-bladder is affected, this elicits severe pain. Another procedure is known as "deep grip palpation." The examiner stands behind the sitting patient, or above the recumbent patient, and forces the fingers under the right costal margin, instructing the patient to take a deep breath; when the gall-bladder is fixed by this method severe pain is experienced.

To test for kidney disorder, the patient is placed on a stool, or lying face downward in bed, with a pillow under the abdomen, so as to make the renal area prominent posteriorly. The left hand is placed flat over the normal kidney and struck forcibly with the clenched right fist. No pain will result. When the test is repeated over a diseased kidney, the patient will cry out with pain.

In cases in which gastro-intestinal perforation is suspected, the "piano" method of percussion will often demonstrate the presence of small amounts of fluid from perforation, and exudates upon hollow viscera; it depends upon the characteristic note which is obtained when the four fingers are struck one after the other and demonstrates the faint flat note coming from the fluid, and which is obscured by the tympanitic note obtained by the ordinary method of percussion.

In palpating for appendicitis, both iliac fossæ should always be palpated at the same time, as only by this means will true difference of tension be detected. W. J. Moore (*Glasgow Med. Jour.*, Apr., 1923).

Simple **empyema of the gall-bladder** is diagnosed by the onset, the location

and character of the pain and tenderness, and by the area and degree of rigidity.

Acute **phlegmonous cholecystitis** and gangrene of the gall-bladder may usually be diagnosticated by the existence of more acute symptoms, more general peritonitis, by the rapid and shallow respiration, location of the pain and tenderness, and by the greater tendency to a rapidly fatal issue.

**Perforated gastrointestinal ulcers** are diagnosticated by predisposing age, history of previous gastric or intestinal disturbances, sudden acute pain in the epigastrium, followed by collapse, and last by the presence of bloody vomiting, or, in the case of intestinal ulcers, by the hemorrhage from the bowel. Perforation occurring in typhoid may be very difficult to tell from a concurrent appendicitis.

**Extra-uterine pregnancy** is to be recognized by the existence of the usual subjective signs of pregnancy, by vaginal examination, and by the absence of inflammatory symptoms prior to the rupture.

**ETIOLOGY.**—Young adults under the 30th year, especially males, constitute the majority of cases. Appendicitis occurs at all ages, however, and is not uncommon in the first two years of life. It is more common during the first six months of the first year and the last six months of the second year.

In 80 cases of appendicitis in infants under 2 years of age collected from literature, 20 cases were under 3 months of age, among which were 2 possible instances of prenatal appendicitis. In children from 3 to 6 months of age there were 6 recorded cases; 11 cases in children from 6 to 12 months; 40 cases in children from 1 to 2 years. Of this number 25 were males, 8 females, and 7 were without record of sex. The blood examina-

tion in almost every case shows a polymorphonuclear leucocytosis. Tenderness at McBurney's point, if it can be elicited, is of diagnostic importance. When there is palpable resistance on the right side, in the presence of other symptoms, the diagnosis of appendicitis should be suspected. I. A. Abt (*Arch. Pediat.*, xxxiv, 641, 1917).

Appendicitis was found more frequently in the army than in civil life. This is probably due to fatigue and exposure to wet and cold, which renders a latent infection acute by lowering the resistance, or it may even give origin to primary acute appendicitis. The crises are particularly severe, but men who are inured to hardships endure these crises often without seeking aid, and such cases arrive at hospitals with fully established diffuse peritonitis and perforated appendices. Rouchier (*Bull. Soc. de chir. de Paris*, xliii, 1846, 1917).

In 131 cases, all but 1 of which were operated by the writer as soon as seen, there were 89 of acute appendicular obstruction, of which 10 showed obstruction only, 18 showed obstruction with a varying amount of gangrene of the wall, and in 59 rupture of the appendix had followed the gangrene. In the obstructive cases the writer holds that the primary cause of the disease is obstruction of the lumen of the appendix. On examination of the appendices removed at operation it was found that obstruction had been due to one of 5 causes: (1) concretions (50 cases); (2) strictures (6 cases); (3) kinks (rare); (4) bands; (5) worms, fruit seeds, and other foreign bodies. S. T. Irwin (*Lancet*, Jan. 18, 1919).

Regarding the sex incidence of appendicitis, the writer found a percentage of 51.5 in men and 48.5 in women among 274 cases of destructive appendicitis and 29.4 in men and 70.6 in women among 659 cases of catarrhal appendicitis. Destructive, gangrenous forms of appendicitis follow the catarrhal process more readily in males than in females because in

the latter the appendix has a better blood-supply, derived not only from the appendicular artery but from vessels in the ovarian and other ligaments. On the other hand, women are particularly prone to the catarrhal processes by reason of their pelvic and abdominal organs. Constipation, usually present in appendicitis, is promoted by their sedentary mode of life. Asthenia is also more frequent in women. W. Backman (*Acta med. scandinav.*, No. 4, 1922).

The conformation of the organ also influences markedly the development of the disease. Its length may vary from a fraction of an inch to 12 inches. It may also point in any direction, though in most instances downward and inward. It is sometimes connected with the ovary by a ligament. Forming, as it does, a more or less long, blind sac, which opens into the cecum, it is more or less exposed, according to the size of its aperture and the direction of the latter, to the penetration of fecal matter, any foreign body the latter may contain, and to kinks, tumors, adhesions, etc., which compress it or obliterate its lumen.

The occurrence of a familial anatomic condition predisposing to attacks of appendicitis in several members of the same family is suspected by the writer. On the basis of 500 cases, among which 50 patients were met with who gave a history of the disease in other members of the family, familial appendicitis appears to comprise 10 per cent. of all cases. This family relationship is most frequent in chronic appendicitis, and especially in such cases does one observe unusually long, large appendices often with dilatation and mobility of the cecum. A relationship between general somatic development and the conformation of the appendix and cecum is suggested by the large proportion of instances of familial appendicitis occurring among individuals of the dystrophic type, with stigmata

of infantilism. Appendectomy in such cases not only eliminates the attacks but favorably influences general strength and development. O. Cignozzi (*Policlinico*, Nov. 15, 1922).

Out of 3000 cases examined as regards the position of the appendix, the writers found the organ postcecal and retrocolic in 2076 cases and pelvic in 825 cases, these two positions thus making up 2901 of the entire series. Their classification of the positions of the appendix recognizes, in addition, the following other varieties: Anterior or preileal; splenic or postileal; subcecal, beneath the caput ceci, and ectopic. The pelvic variety of appendix is on the psoas muscle, either near or hanging over the brim of the pelvis. Gladstone and Wakeley (*Brit. Jour. of Surg.*, Jan., 1924).

While the entire sac is lined with lymphoid tissue, an accumulation of the latter at the orifice forms what has been termed Gerlach's valve. Its functions are not known.

Various diseases favor the development of appendicitis: gastrointestinal disorders, influenza, typhoid fever, and particularly constipation and cold. The local inflammation may be caused by the intrusion of: micro-organisms, specific and non-specific; constipation, dietetic indiscretions, and the habitual use of meat. Compounds of saturated fatty acids have been urged as etiological factors. The rarity of appendicitis in the Chinese appears, according to Matignon, to confirm the opinion of Keen and Lucas-Championnière as to the predisposing influence of meat diet, meat in China being a luxury within the reach of few.

Appendicitis often occurs in the course of general infections, influenza, scarlatina and typhoid fever in particular, infection being probably transmitted through the blood. The primary site of infection, however, is located in the tonsils, which, like the

appendix, are in part made up of lymphoid tissue. Guerra (Cron. med. chir. d. l. Habana, Jan., 1922).

Appendicitis is often tuberculous, usually as a condition secondary to a focus in the lungs. Of 200 cases in private sanatoriums, 12.5 per cent. had had appendectomies; in a public sanatorium, 6 per cent. Appendicitis is often followed by ill health culminating in active lung disease. A careful history and physical examination, with X-rays if possible, should be made of all patients to be operated on, to discover any active or latent lesion. Ether should not be used in such cases, and convalescence should be prolonged to avoid subsequent activation of any lung lesion. A. Armstrong (Atlantic Med. Jour., Apr., 1923).

The appendix may be involved in pelvic inflammation and its resistance lowered. The work of Rosenow shows that appendicitis is not caused by the colon bacilli, but usually by streptococci of much the same type as inhabit the crypts of tonsils and the apical abscesses of teeth. The inflammatory exudate becomes infected, secondarily, by the colon bacilli in cases of perforating abscessed appendix. C. H. Mayo (Jour. Amer. Med. Assoc., Aug. 23, 1924).

A man aged 37 developed appendicitis during the height of an attack of streptococcic tonsillitis. Abdominal pain and sore throat had developed 30 hours before his admission to the hospital. The temperature was 103° and leukocyte count, 21,800. A perforated gangrenous appendix with general suppurative peritonitis was found; recovery followed. Blood culture was negative, but the culture from the appendix showed streptococci, coliform bacilli and diplococci. The route of infection in such cases is usually the blood-stream.

Appendicitis accompanying or following influenza has been not uncommon, and Behrend has reported 8 such cases, who had been in bed 4 days before the appendix symptoms developed; he operated on 3 cases.

Appendicitis should be suspected in intestinal influenza upon the appearance of persistent lower abdominal pain with tenesmus; localized tenderness; dullness in the flanks, and increasing leukocytosis. J. O. Bower (Med. Jour. and Rec., Jan. 21, 1925).

Of late, tonsillitis and pus-laden tonsillar crypts, parotitis and streptococcic disorders of the teeth have been incriminated.

Case of appendiceal abscess in which the infection probably came from the roots of the teeth, the culture from the pus evacuated from the peritoneal cavity having been a pure culture of *Streptococcus viridans*. Markoe (Bull. Lying-In Hosp., City of N. Y., May, 1917).

Rosenow demonstrates the fact that the streptococcus group has an elective affinity for certain tissues. The writer adduces further data which tend to prove that acute appendicitis is an acute metastatic focal infection in many instances. Out of 236 cases, 214, or 91 per cent., were primary attacks; 22, or 9 per cent., were recurrent. Of the 214 cases, in 183, or 86 per cent., there were definite primary infections of the upper respiratory tract. There was no such evidence in 31, or 14 per cent. The respiratory infection preceded the appendiceal attack on an average of sixteen days, the extremes being one and sixty days. The appendicitis most usually followed the subsidence of the constitutional symptoms accompanying the nasal or throat infections. J. S. Evans (Wisc. Med. Jour., xvii, 91, 1918).

Stress laid on the association of nasal accessory sinus infection with appendicitis. Of 90 cases seen by the writer, 14 had undergone appendectomy. P. Watson-Williams (Pract., Apr., 1921).

The possibility of an endemic incidence of appendicitis, due to direct transmission, is regarded favorably by the writer. Studying the family history of 275 operated cases, he found that 151 cases, or 54.9 per cent., were paralleled by cases in the

patient's vicinity; 175 cases were noted in the family of the patient, 44 among relatives and servants, and 26 among persons with whom the family came in daily contact. Thus, 151 operative cases were associated with 245 cases in the immediate vicinity. In the majority of instances the intervals between the corresponding cases were relatively long, but in some the interval between cases within the same family was but a few months or even days. He thinks prophylactic measures may reduce the transmission and incidence of the disease. A. Fonio (Schweiz. med. Wochenschr., Oct. 11, 1923).

Neighboring catarrhal, pelvic, typhoid, and tubercular processes; constriction, torsion, or strain have also been enumerated.

Following 896 laparotomies for gynecologic disease, concomitant appendix disease, present in 16.4 per cent., was found to be secondary to the gynecologic lesions in most instances. Lesions were found in the appendix in 75 per cent. of the cases of torsion of a cyst in the right ovary, and in 23.7 per cent. of the cases of right tube or ovary disease, but never with left tube or ovary disease alone. While simple congestion in the appendix with gynecologic disease does not alone warrant appendectomy, systematic investigation of the right tubes and ovaries as a routine measure in all cases of appendicitis should always be carried out. Waegeli (Corresp. bl. f. schweizer Aerzte, Aug. 24, 1918).

The writer describes 11 cases of torsion of appendices epiploicae which had been under observation in the Mayo Clinic in the past 10 years. Seven of these cases were true torsion of the appendix epiploica; one was of doubtful torsion, acting as a band producing intestinal obstruction; two of incarceration in a left inguinal hernia, and one of a foreign body in the peritoneal cavity with unproved origin from an appendix epiploica. Four of the cases of torsion

presented acute symptoms, for which operation was done, and in the remaining 3 cases the torsion was probably symptomless, as it was found in the course of abdominal operations for other pathologic conditions. Hunt (Annals of Surg., Jan., 1919).

Mechanical factor in the production of appendicitis emphasized. In early cases the author has found the appendix either partly or completely twisted. The edema and congestion of the organ varied with the severity of the twist. Usually the torsion appeared to be from left to right, the mesentery becoming wrapped around the appendix. The amount of torsion ranged from a slight twist to complete strangulation and indentation of the peritoneal surface of the appendix by the tightened band of mesentery. Further twisting of the organ will produce subsequent attacks, constituting "recurring or intermittent typhlitis," until finally the strangulation may become complete and urgent symptoms arise. If the adhesions produced in slight torsion are adequate to prevent free movement of the appendix, no further rotation will occur and the condition remain unchanged or gradually subside. E. J. L. Jones-Evans (Pract., Feb., 1925).

Cases due to actinomycosis and various parasites are occasionally observed. Appendicitis may be caused by ova of the *Ascaris lumbricoides* and *Trichocephalus dispar*. The removed appendix has also been found to contain ova of *Bilharzia hematobia*. The stools should, therefore, be examined for worms or their ova.

Oxyuris is regarded as a common cause of appendicitis by the writer. Out of 60 excised appendices he found oxyurids in 24; in 7 of these cases the parasites were present elsewhere in the intestine. Often the pains diagnosed as chronic appendicitis are worm pains, and many of the appendices removed in such cases show no pathologic changes. The

pains are probably due to irritation of the nerve-endings in the appendix and intestinal mucosa by metabolic products of the worms; the narrow appendix is a much more favorable location for absorption of these products than any other portion of the bowel. Women suffer from the worm pains 3 times as often as men. Secondary infection of the lesions caused by the parasites results in acute suppurative appendicitis. Prophylaxis of appendicitis by giving anthelmintics (provided no inflammatory symptoms are present) is feasible, though no effectual remedy for oxyuriasis is as yet known. Rheindorf (Mitteil. a. d. Grenzgeb. d. Med. u. Chir., No. 4, 1922).

Examining 50 appendices from the postmortem room, the writer found oxyuriasis in 28 per cent. On the other hand, in the appendices from 73 cases of appendicitis of unknown etiology oxyuriasis were found in but 19.2 per cent. Thus, no evidence could be obtained that oxyuriasis is frequently a cause of appendicitis. E. H. Eastwood (Jour. of Pathol. and Bacteriol., Jan., 1923).

Traumatism, blows upon the abdomen, etc., sometimes produce inflammation of the appendix, probably, however, only when the organ has already been the seat of some lesion or so disposed anatomically as to receive the blow directly.

A study of 1400 cases by J. B. Deaver showed that trauma was never the direct exciting cause of acute appendicitis in a perfectly normal appendix. An acute attack of appendicitis can follow a severe blow upon the abdomen or fall thereon, or may be the result of muscular contractions of the iliopsoas muscle in an appendix which has been previously inflamed only under the following conditions: In a latent or residual abscess or extensive pathological lesion of the appendix, where the appendix does not occupy a deep pelvic position, but is in close proximity to the anterior abdominal wall, severe direct traumatism may precipitate an acute attack.

Strong contractions of the iliopsoas muscle cannot be the immediate cause of an acute attack of appendicitis where the appendix is chronically diseased or where it has extensive pathological lesions, unless it is firmly adherent, and not simply in apposition, to the peritoneum overlying this muscle. Traumatism, to be a factor in the causation of appendicitis, must be direct and of considerable force. Such force, applied to the right iliac fossa, may tear the underlying parietal peritoneum and so simulate an acute attack of appendicitis that only opening the abdomen and exposing the appendix could definitely settle the matter. The mortality is very high in these cases on account of (a) the failure to recognize the condition until the disease is well advanced; (b) the rapid gangrene and perforation which occurs, and (c) the delay in operation. Immediate operation is indicated. EDITORS.

Case of a boy 11 years of age, who had been struck on the abdomen by a plank. Immediately after the accident he suffered severe pain and was placed in bed; the pain subsided in a couple of hours, and the 2 days following he was able to walk about the house. The pain then became much sharper and physic was administered, and a physician called. The boy was sent to the hospital with a diagnosis of appendicitis. Seven days after admission he showed a slight temperature indicative of sepsis, and operation was decided on. The cecum being freed externally, about an ounce of thick, foul-smelling pus was found, containing 2 scybala. There was no trace of the appendix except a great amount of tissue debris, and a large hole in the cecum. The hole in the gut was sutured and the cavity drained through the posterior abdominal wall. Recovery followed. The etiology is explained thus: The plank, striking the abdominal wall, tore the appendix from its meso; some reaction followed, then subsided until the appendix, deprived of its blood supply, began to slough off and give rise to the symptoms which led to operation. A. L. Soresi (Med. Rec., Apr. 23, 1921).

Case of a man aged 22 years who, three minutes after a violent lifting effort, felt a sharp pain across the lower abdomen and vomited. Severe pain continued and there was further vomiting. Tenderness over the whole of the lower abdomen, especially at McBurney's point, and rigidity were noted two days later. On opening the abdomen a short, acutely inflamed appendix was found buried in adhesions behind the cecum. There was free pus in the peritoneal cavity. C. J. G. Taylor (Brit. Med. Jour., Jan. 6, 1923).

trate into the interior of the appendix through deficient actions of a valve which usually closes its opening, or on account of excessive patency of the latter.

Kelly states that in 1000 cases operated upon in Johns Hopkins Hospital in only four instances were foreign bodies found. He quotes 2527 cases with but 10 due to the presence of foreign bodies—only  $\frac{2}{100}$  of 1 per cent. of the entire number. Murphy found foreign bodies present in 3.5 per cent. of his cases, while Fitz and Matter-



Appendix containing hardened fecal masses. (J. F. Pilcher.) (New York Medical Record.)

It is generally agreed that trauma does not initiate an original inflammation in a healthy appendix. The conditions favoring a traumatic appendicitis are: An appendix with its lumen obstructed by a coprolith; with fecal stasis in, and defective drainage of, the distal segment; with increased virulence of the contained organisms, on account of their confinement. These factors bring about an immediate, destructive invasion of the appendix wall. N. A. Ludington (Jour. Amer. Med. Assoc., May 19, 1923).

Irritating fecal matter frequently forms hard, egg-like fecal concretions of various sizes. Foreign bodies—cherry stones, orange seeds, buttons, spicules of bone, pins, etc.—may pene-

stock found them in 12 per cent. of their perforative cases. Ranvier discovered 16 foreign bodies in 439 post-mortem examinations, or 3.5 per cent. of the cases. It is probable that all cases, perforative and non-perforative, will show but from 2 to 3 per cent. as due to the irritation and actual trauma induced by the presence of foreign bodies. To this may be added the slightly larger percentage arising from the presence of fecal concretions (ster-coral appendicitis). When these cases are included, it will be found that about 12 per cent. of the patients operated upon may be grouped under the so-called traumatic class. J. D. Robertson (Surg., Gynec., and Obstet., Oct., 1911).

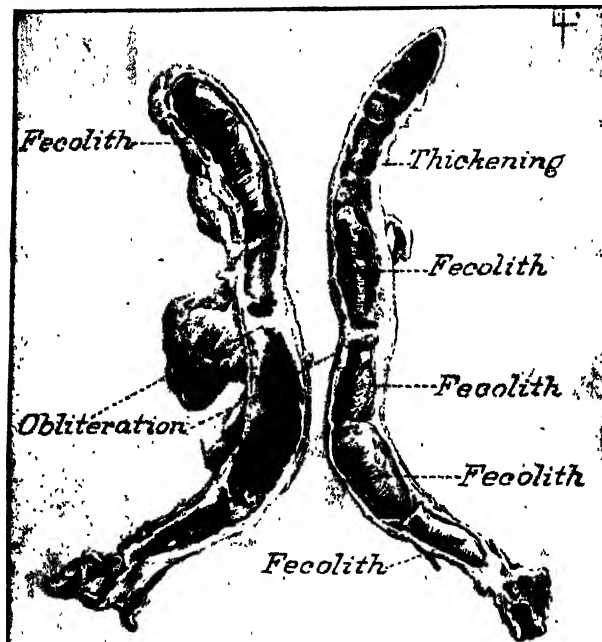
Foreign bodies are present in the appendix in about  $2\frac{1}{2}$  per cent. of op-



erated cases. More than 52 per cent. of them are pins, often swallowed by children. R. H. Fowler (Long Island Med. Jour., Dec. 1914).

In 400 operations on the appendix the writer found a foreign body in 10 cases. In 6 there was a living oxyuris, 4 of these patients being girls between 6 and 17; in others a hair, part of the head of an oat, a sliver of wood, a grapeseed, a blackberry stone or

in an irregularly concentric arrangement was found in an appendix by the writer. It measured 4 x 1 centimeters and was presenting at a ragged hole in one side of the organ. The appendix was very large and was densely adherent in the depths of the iliac fossa. Surprisingly often, one finds as the nucleus of a fecal concretion such objects as shot, pins, glass, egg-shell, bits of enamel, hair, bristles,



Section of appendix containing hardened fecal masses. (J. F. Pilcher.) (New York Medical Record.)

small shot. Grondahl (Norsk Mag. f. Laegevidenskaben, Dec., 1915).

Grape seeds were at one time thought to play an important rôle as etiological factors, but a painstaking investigation by Edmund Andrews showed that this was not based on facts. Indeed, it is quite probable that foreign bodies play a very small part in the production of attacks of appendicitis, excepting hardened fecal masses.

A porcelain-hard concretion consisting of dried fecal matter and bile salts

bits of wood, gallstones, pin worms, cherry stones and the seeds of grapes, raspberries, strawberries, caraway and figs. H. Packard (Boston Med. and Surg. Jour., Dec. 1, 1921).

Case of a man aged 43 complaining of general abdominal pain and vomiting. Two years before, he had been examined with the X-rays for gastric ulcer. The appendix was removed, and contained a yellowish calculus 4 x 1.5 centimeters in size consisting apparently of bismuth enclosed in a membranous capsule. Müllender (Zentr. f. Chir., Mar. 10, 1923).

**PATHOLOGY.**—The vermiform appendix is a glandular organ presenting a certain analogy to the tonsils and liable, as well, to follicular, mucous, submucous, infectious, exudative, and ulcerative disorders.

Examination of 1500 specimens led the writer to conclude that there is no pathological evidence that an acute catarrhal appendicitis occurs, nor is there evidence of "involution" nor of "chronic catarrhal" inflammation of the appendix. The only justifiable classification of inflammation of the appendix is: (1) Acute appendicitis; (2) healing or subacute appendicitis; (3) healed or chronic appendicitis. Acute localized peritonitis is always present in acute appendicitis as early as 12 hours after the onset; the absence grossly of a localized peritonitis in suspected cases is *ipso facto* evidence of absence of acute appendicitis. In addition to obliteration and stricture, attention is called to 2 new, constant and pathognomonic signs of chronic appendicitis, namely: (1) absence of mucosal crypts, and (2) marked widening of the submucous connective tissue zone. The latter is especially easy to determine in cross sections. Moschowitz (Annals of Surg., June, 1916).

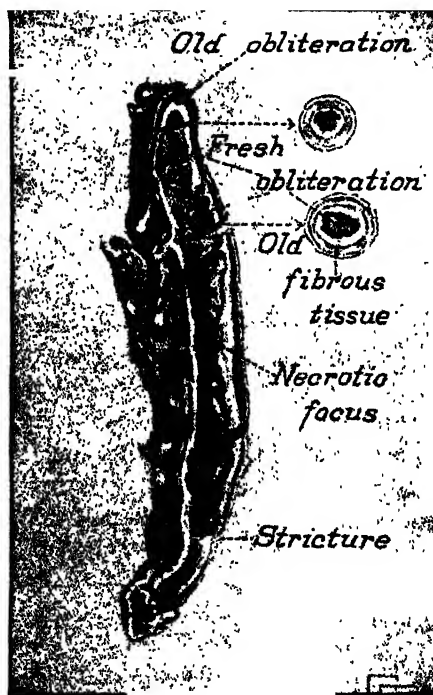
Acute appendicitis is not a specific disease due to a single organism, such as a streptococcus, as is sometimes asserted. It may be caused by a variety of organisms.

Out of a series of 66 cases studied bacteriologically and histologically, *B. coli* was found alone in 25 appendices and in combination with other organisms in 12. *Streptococcus hemolyticus* occurred alone in 6 and with *B. coli* in 9. *B. proteus vulgaris* and *B. pyocyaneus* were each found 5 times. There was a scattering of other organisms. All early lesions were seen at the margin of the lumen of the appendix. The inflammatory reaction does not vary with the type of organism, although it is perhaps more hemorrhagic where the hemolytic streptococcus is present. The delicate Gram-positive bacillus

described by Aschoff was not found in the lesions.

In a 5-year old girl, a case of pneumococcus Type I, peri-appendicitis was succeeded in 4 days by lobar pneumonia, likewise due to pneumococcus Type I. The evidence is against a hematogenous origin of acute appendicitis. S. Warren (Amer. Jour. of Path., Mar., 1925).

The colon bacillus has been held generally responsible for appendicu-



Section of appendix showing areas of obliteration and necrosis. (J. F. Pilcher.) (New York Medical Record.)

lar inflammatory processes. The work of Rosenow, however, suggested that streptococci are frequently the cause, the colon bacillus constituting a secondary infection. In a smaller proportion of cases other organisms are present.

In 30 per cent. of the cases of acute appendicitis seen at the beginning of the attack by the writer, the

mucosa of the appendix was found destroyed during the first day, and in 70 per cent. after the second day of the attack. Due to loss of this protective barrier the wall of the appendix is invaded by the putrefactive bacteria. Gangrene developed on the second day in 46 per cent. of the cases, on the third day in 53 per cent., and on the fourth day in 65 per cent. A purulent peritoneal exudate was found in 18 per cent. on the second day and in more than 40 per cent. on the third and fourth days. He observed that a leucocytosis of 20,000 tended to confirm the diagnosis. The course was generally determined during the first 2 days and it is only during this short interval that expectant treatment may be employed as a means of arriving at a diagnosis. After this period, temporizing may be fatal. E. Kummer (Rev. méd. de la Suisse Rom., xl, 133, 1920).

Various forms of appendicitis have been described, but these are in reality stages of the fully developed morbid process. The mildest, or *simple catarrhal*, form is usually caused by constipation or an indiscretion in diet, in which the inflammatory process, after passing through an acute stage, including more or less epithelial desquamation, excoriation, etc., and involving the mucosa, submucosa, and the serous layer and the overlying area of peritoneum, gradually recedes. The appendix remains very vascular and functionally weakened, and is subject to renewed attacks of inflammation.

Microscopic examination of 539 appendices removed during or within 10 days after an acute attack, together with the gross pathology in over 500 cases by the writer, showed that during the first 24 hours of an attack the pathological changes are similar in nearly all cases, a definite obstruction of the lumen of the appendix being always present, distally to which the organ is distended. Following on the first 8 or 10 hours,

fibrin is found on the peritoneal surface, and toward the close of the first twenty-four hours a considerable proportion of the appendices show commencing gangrene macroscopically. Surgically, the peritoneal involvement of the first day may be ignored and the abdomen closed without drainage. On the second day, owing to coalescence of microscopic necrotic areas, macroscopic areas of gangrene are noticeable, and perforation, if it is going to occur, usually takes place on this day. In the majority of cases there is now a definite fibrino-purulent exudate on the peritoneal surface. By the third day destruction has usually reached its maximum, evidence of commencing repair now appearing in the presence of fibroblasts in all sections. On the fifth day in the non-gangrenous cases, the polynuclear leucocytes have almost disappeared. Protection of the peritoneal cavity in appendicitis depends upon maintenance of the fibrous periappendicular adhesions rather than upon the bacterial impermeability of the appendicular walls. The writer agrees with Deaver, Moynihan, Ochsner and others that clinical perforation would almost never occur if the practitioner and laity would appreciate that in appendicitis "perforation spells purgation" and withhold cathartics during the early stages of suspected cases. Stanton (Amer. Jour. Med. Sci., Apr., 1915).

The writer recognizes 4 types of appendicitis. The first, the most common, is that of fibroid degeneration in the walls of the appendix. This is not an infectious process but rather an irritative one, due to the contraction of the hyperplastic connective-tissue upon the nerve-endings in the appendix. The next most common form is the acute intrinsic infective type. The third is the extrinsic infective type, the complement of extensive infection in the neighborhood, such as pyosalpinx or ovarian abscess. The fourth type the writer adds is the syncongestive form. Appendix symptoms in such

instances are probably due to the fact that the soft inner coats of the appendix find difficulty in swelling within the light outer sheath. R. T. Morris (Med. and Surg., i, 91, 1917).

The *ulcerative*, or *perforative*, variety causes many complications, including abscesses in other, even remote, structures, as will be shown presently (p. 107). In this form the inflammation is often initiated by fecal concretions or foreign bodies, and gradually proceeds to ulceration. An opening is created by the ulceration, and the fecal concretion or foreign body escapes, with the septic discharges formed, into the abdominal cavity. Often, however, the perforation is at a point other than that occupied by the fecal concretion.

The writer classifies appendicular abscesses as follows: (1) in front of, below, and outside of the cecum, the pus being confined by the cecum, small bowel, omentum, etc.; (2) outside the cecum and ascending colon or behind the cecum in the layers of the mesocolon; (3) in the pelvis; (4) near the median line to the median side of the cecum; (5) free in the abdominal cavity or in many pockets between the coils of intestines. In addition there are seen secondary abscesses close to the original abscess, residual abscesses at the site of the primary abscess, and metastatic abscesses at distal points or as a parotid abscess, pyelephlebitis, etc. Deaver (N. Y. Med. Jour., Feb. 5, 1916).

In 146 cases collected by Matterstock perforation was found to have occurred 132 times. Properly treated, however, every case of appendicitis should be operated upon before perforation has occurred. Ulcerative appendicitis may also occur in the course of an infectious disease, especially typhoid fever.

If, however, through previous local inflammation, close adhesions have united the appendix and the parie-

tal peritoneum, the appendiceal contents may pass entirely through the peritoneal coats. This gives rise to an extraperitoneal abscess, which may open externally above Poupart's ligament or within the abdomen into the small intestine, the bladder, the vagina or the rectum, the portal vein, iliac artery, etc.

Pleurisy, to which reference has already been made, is due to propagation of the pyogenic process through the retroperitoneal cellular tissue, or through the lymphatic system. It often passes unperceived, is almost invariably on the right side, and is rarely bilateral.

If there are no adhesions between the appendix and the parietal peritoneum suppurative peritonitis is produced, and this process usually gives rise to a protective plastic exudation, which causes the surrounding loops of small intestine to adhere together and inclose the secondary abscess, thus temporarily protecting the surrounding parts.

If, however, the plastic inflammation does not induce protective adhesion between the intestinal loops, the septic material invades the whole peritoneal cavity, and gives rise to diffuse, and often fatal, peritonitis.

In about 20 per cent. of cases a retrocecal appendix exists. The simplest form has the usual mesentery, and differs from the normal only in its position and course. The second variety passes up outside the colon, beneath the peritoneum of the lateral iliac or lumbar fossa, is without a mesentery, and is retroperitoneal, except anteriorly and at its tip. The third variety passes up along the cecum and colon, and its peritoneal covering is that of the colon wall. The fourth variety (rare) passes up beneath the cecum and ascending colon between the layers of the mesocolon, and is a true retroperitoneal appendix. The sequelæ in retrocecal appendicitis, occurring in the

event of failure of early diagnosis or inadequate treatment, are of a special type. Peritonitis extends and is usually confined to the lateral or lumbar peritoneal fossa, outside the colon, but may extend up toward the kidney, liver, gall-bladder or even into the lung. Cases with direct extension may point over the iliac crest, in the lumbar region, or through the cellular tissue down over the buttocks to the knee. In the fourth variety a septic thrombophlebitis may occur and reach the liver, causing abscesses therein. The symptoms at first are the same whatever be the position of the appendix, but the peritonitis in retrocecal cases is more localized and may quickly disappear. A valuable sign, however, is that deep pressure over the iliac crest or in the lumbar fossa elicits a very distinct tenderness, previously unsuspected by the patient. Proper diagnosis requires: (1) An accurate, detailed account of the symptoms of the first 24 to 48 hours; (2) realization that the later signs are chiefly those of peritonitis, largely limited in these cases to the outer side and back of the cecum; (3) the evidence of continued infection; (4) slight stiffness and distinct tenderness on pressure above the crest of the ilium in the lumbar region. The treatment of retrocecal appendicitis is the same as that of any other type. Early diagnosis and early operation are important. J. N. Jackson (Southern Med. Jour., Apr., 1923),

When, as occasionally happens, the abscess rids itself of its contents, pus, blood, feces, detritus, etc., into the cecum, the acute process ceases, the patient proceeding either to recovery or lapsing into *chronic appendicitis*, with its chain of recurrent attacks. The appendix may also be the seat of areas of fibrosis, causing strictures, etc., sufficient in some instances to obliterate completely (*obliterating appendicitis*) its cavity. Or, the stricture may block off a point of the latter, and the distal

cavity become the seat of an accumulation of thick fluid or mucus (*appendiceal mucocoele*).

The most threatening complication, *gangrenous appendicitis*, may occur as a complication of either of the above conditions or of arrest by kinking, thrombosis, pressure upon, or any other obstructive agency of the supply of arterial blood to the organ. In most instances of gangrene, especially when the appendix is found moist, green or black, greatly swollen and soft, or even detached from the cecum, an overwhelming local infection is probably the initial factor. Fortunately, where the inflammatory process reaches beyond the appendix proper, adhesions are apt to form around the diseased organ. These adhesions afford protection to the surrounding structures by the time perforation or gangrene occurs. The gangrenous areas are well shown in the annexed colored plate published with an article on the acute form by the late Professor Kocher.

An anaërobic streptococcus corresponding culturally to the *Streptococcus putridus* is instrumental in causing general symptoms as well as local tissue disease, including gangrene, in a considerable proportion of cases. It produces thrombophlebitis and liberates malodorous gas. In cases infected with it, resulting in a foul exudate, drainage is necessary, whereas in the presence of a seropurulent or purulent exudate which is free of odor primary closure of the wound is feasible. In odorless seropurulent exudates *Bacillus coli* infection was found in 61 per cent. of cases, while in 14 per cent. the exudate was sterile. H. Brütt (Beitr. z. klin. Chir., No. 1, 1923).

The abscess does not always open inwardly, *i.e.*, into a neighboring intestinal cavity or the peritoneum; it may open through the abdominal wall.



Acute Gangrenous Appendicitis. (*Kocher.*)

Correspondenz-Blatt für Schweizer Aerzte.



**PROGNOSIS.**—Death may occur very early, especially in children, who are also more liable to peritonitis than adults. The danger of death is greater in men than in women.

In the writer's 300 operative cases of appendicitis there had been 16 deaths from all causes, or 5.3 per cent. The author divides the cases into 4 classes: Class I. Appendix acutely inflamed or gangrenous, but with no pus outside the appendix, 59 cases, with 3 deaths. Class II. Acute cases with localized abscess, 64 cases, with 2 deaths. Class III. Acute cases with free pus, 20 cases, with 9 deaths. Class IV. Chronic or recurrent cases, 157 cases, with 2 deaths. The fatal cases he divided into 4 groups as follows: Group I. Recovery from operation and death later from pulmonary embolism, 2 cases. Group II. Death due to accidents and previous diseases, 2 cases. Group III. Cases making good recovery from operation and ending fatally afterward from pulmonary infections, 3 cases. Group IV. Cases making a good operative recovery, but ending fatally some time later on account of exhaustion due to fecal fistula, 3 cases. Group V. Cases ending fatally with immediately continuing symptoms of abdominal sepsis, 6 cases. Wainwright (*Surg., Gynec. and Obstet.*, Nov., 1911).

The following conclusions regarding the prognosis of acute appendicitis are now accepted by most surgeons: (1) The mortality in cases operated upon during the first 24 to 36 hours is almost *nil*. (2) Cases without peritoneal involvement localized to the immediate vicinity of the appendix can be operated safely at any period of the attack by a competent surgeon. (3) In cases with early peritonitis of greater or less extent the mortality rises rapidly in cases operated upon after the first day of the peritoneal involvement. (4) Late abscess cases should not be over 5 or 6 per cent. (5) The bulk of the operative mortality today occurs in the severe cases operated in

the intermediate stage of the attack, when there is well-marked peritoneal infection of more than 24 hours' duration. E. M. Stanton (*N. Y. Med. Jour.*, Sept. 26, 1914).

In 822 cases at the Cook County Hospital, general peritonitis still proved the most frequent complication of acute appendicitis. In some cases this complication seemed to have been dependent on the too early removal of the drain in abscess cases. Early operation means low mortality. Abscess formation may be considered as evidence of resisting power on the part of the organism. There was a 2.2 per cent. mortality in abscess cases against a 5.5 per cent. mortality in gangrenous cases without abscess formation. More (*Jour. Amer. Med. Assoc.*, Mar. 24, 1917).

In a study of the statistical reports of several large hospitals in Greater New York, the writer found the mortality of appendicitis to be about 16 per cent. Deaths were principally due to general peritonitis, suppurative peritonitis, and a moribund condition on admission. He condemns the prolonged use of the ice-bag, and regards intestinal fistula one of the dangerous sequelæ. He formulates the following dicta: In so-called fulminating and late cases study well the pathology of the caput coli and the adjacent tissues about the appendiceal base. If bacteria have necrosed the tissues about the appendiceal base, excise the stump and treat the rent as in gastric ulcer, placing a Mikulicz drain over the Lembert sutures, provided the patient's condition will permit the work. In obstinate fecal fistula following appendicitis, resect the cecum and anastomose the small intestine laterally with the cecum. As a large proportion of fecal fistulæ following appendicitis close spontaneously, unless of the dangerous variety requiring immediate attention, one should wait from 3 to 5 months for this spontaneous cure. J. C. Kennedy (*L. I. Med. Jour.*, Jan., 1921).

In the Registration Area of the United States, in the 5-year period



1901 to 1905 the mortality rate for appendicitis was 11 per 100,000 of population. In the next quinquennial period it rose to 11.2; from 1916 to 1921, to 12.4; in 1920, to 13.4, and in 1921, to 14.4. In a series of patients observed during the years 1901 to 1905 and treated conservatively, Ochsner reported a mortality of 4.1 per cent. Recently, Gatch reported a series of cases treated by modern methods with a mortality of 8.7 per cent. The annual toll taken by appendicitis almost equals the combined total of intestinal obstruction, gall-stones, and gastric and duodenal ulcer. Up to the age of 45 there are a few more deaths from appendicitis than there are from cancer. A. M. Willis (Va. Med. Mthly., Apr., 1925).

For patients operated on the first day of illness the author's statistics show a mortality of 1.2 per cent.; on the second day or in the interval, 2.4 per cent., and between the seventh to the tenth day, 9.6 per cent. Among 72 cases treated by medical measures exclusively, either because of mild illness or on account of complications and weakness, the mortality was 2.7 per cent. In conclusion, early operation is advised. G. Hotz (Schweiz. med. Woch., Jan. 9, 1926).

Improved methods of treatment of acute appendicitis, especially early operation as soon as the diagnosis has been made, have brought the mortality down from 30 per cent. to 2 or 3 per cent. Some operators claim as low as 1 per cent. when early operation can be resorted to. A local abscess raises this to an average of 8 per cent., and where peritonitis has developed, considerably higher; from 5 to 25 per cent., according to various statistics.

In 1700 operations for acute appendicitis operated by the writer there were 66 deaths, a mortality of 3.7 per cent. Of the complications, fecal fistula occurred in 42 cases, secondary abscess in 30 and intestinal obstruc-

tion in 27 cases. An analysis of the cases of obstruction shows that fully 70 per cent. required drainage at the original operation. There is no doubt that in every case of acute appendicitis requiring drainage operation was delayed beyond the most favorable moment. J. B. Deaver (N. Y. Med. Jour., Mar. 8, 1919).

In a study of the mortality and complications of 584 consecutive cases of acute appendicitis, the writer emphasizes the importance of early operation. Thirty-five per cent. were late cases in which either a localized abscess or diffuse spreading peritonitis had developed before the patient's admission to the hospital. The mortality was no lower in the abscess cases than in those of appendicitis with free fluid, and in the former the secondary complications and late sequelæ were greatly increased. The outlook is therefore more favorable in early cases in which closure without drainage is possible. In cases without drainage the mortality was 0.83 per cent., and in drained cases it was 6.8 per cent. F. W. Bancroft (Jour. Amer. Med. Assoc., lxxv, 1635, 1920).

In a series of 1000 operative cases of appendicitis, nearly two-thirds were acute. Among the acute cases the mortality was 4.7 per cent. In cases without perforation, it was 1 per cent.; in perforated cases operated on within the first 24 hours, 4.7 per cent., and in perforated cases operated on later, 12 per cent. In 68 cases of appendix abscess in which the writer waited for complete walling off before operating, the mortality was 2.9 per cent. In 28 cases of diffuse peritonitis treated by irrigation with physiologic salt solution the mortality was 64 per cent. Cases with perforation were merely drained, without irrigation; the main causes of death in these cases were diffuse peritonitis and, less frequently, pulmonary embolism. Fecal fistulas developed in 6 cases, all of which recovered by spontaneous healing of the fistula. Cases of abscess

of the abdominal wall were commonest where the wound was closed without drainage, and numbered altogether 21. In 5 cases fixation of a movable cecum proved necessary. In 7 cases exhibiting but slight changes in the appendix oxyurids were found in the organ. H. Steichele (*Beitr. z. klin. Chir.*, No. 3, 1922).

The average hospital mortality rate for appendicitis is slightly over 10 per cent. That it is so high is due to a considerable extent to procrastination. Responsibility in insisting upon early operative treatment falls on the general practitioner, who sees most of these cases first. This is particularly so because, whereas the initial symptoms of appendicitis are clean cut and almost unmistakable, the later symptoms are equivocal and unreliable. A. S. Risser (*Jour. Okla. State Med. Assoc.*, Jan., 1923).

The end-results in patients who recover from operations for acute appendicitis are almost uniformly good, but the mortality rate for such operations ranges from 3 to 6 per cent. This high operative mortality (as well as the high post-operative morbidity in cases of chronic appendicitis) are due in large measure to the common belief that in every case the only proper procedure is the removal of the appendix. Both the laity and medical profession should realize that acute appendicitis with associated peritonitis is a systemic rather than a local disease. More stress should be laid on the treatment of the peritonitis. The mortality in acute cases will be greatly reduced by the application of the Ochsner treatment before operation, the Fowler position after operation, and the Alonzo Clarke treatment for peritonitis, together with the application of large hot packs over the abdomen and hypodermoclysis. In operating, the writers adopt Crile's principle of limiting the primary procedure to incision and drainage if the appendix is not readily accessible, postponing the removal of the appendix and exploration until the acute stage is past. W. E. Lower and T. E.

Jones (*Jour. Amer. Med. Assoc.*, Aug. 25, 1923).

Cases of simple catarrhal appendicitis with adhesive peritonitis almost invariably get well. Those in which extra-peritoneal perforation occurs generally recover, unless the abscess opens into the bladder or the pleura, when recovery is doubtful. When perforative peritonitis occurs, however, the chances of recovery are greatly reduced.

In children the prognosis is, as a rule, favorable if operative procedures are resorted to early. A peculiarity in them is that the case becomes rapidly worse if left untreated. Operation during the interval is practically free from risk in patients in poor condition.

Tendency to recurrence is one of the marked features of appendicitis. The danger to life increases with each successive attack.

Adhesions after appendectomy may induce pain, acute intestinal obstruction with or without strangulation or incarceration, and chronic intestinal stricture. Pain is likely to appear earliest in cases in which primary closure of the wound has been feasible or in which the inflammation has extended beyond the confines of the appendix. X-ray study with opaque meals and enemas is indicated in all doubtful cases. Often, however, the symptoms are due, not to adhesions, but to alternating constipation and diarrhea the result of a functional or inflammatory catarrhal condition which usually has already been present before the operation. Among other possible causes of pain after appendectomy are gastric or duodenal ulcer, gallstones, adnexal diseases, pyelitis, and nervous disturbances. L. Kuttner (*Deut. med. Woch.*, xlviii, 1604, 1922).

The many rapid perforations followed by spreading peritonitis account for the high death rate of acute appendicitis in infancy. Perforation is often precipitated by cathartics. Beekman (*Ann. of Surg.*, Dec., 1924).

**MEDICAL TREATMENT.**—Medical treatment is indicated in only two conditions; (1) when operation is absolutely refused, and (2) while endeavoring to establish the diagnosis.

The best results in acute appendicitis can be obtained only by operating immediately after the onset of the disease, before any purgative medicine has been given and before peritonitis has occurred. Practically, if not actually, all the patients with perforative appendicitis seen by the writer have been purged. He considers it practically criminal to administer a purgative in an "acute abdomen" until the cause is determined; but one drug that he knows of can be of use, namely, morphine, and this should not be given until the diagnosis is made. J. B. Deaver (*N. Y. Med. Jour.*, Feb. 10, 1912).

For travelers in localities lacking experienced surgeons and hospital facilities, the essential features of medical treatment in appendicitis are **dorsal decubitus, liquid food, enemas of warm water, egg yolk, and sweet oil, warm flannels wrung out of alcohol and water and applied to the belly, covered with rubber tissue, and renewed when dry, and codeine tablets**  $\frac{1}{10}$  grain (0.006 Gm.) every 2 hours until pain is notably less, then less frequently. Transport from the bed or sitting up is forbidden so long as pain continues. **Cracked ice and good brandy** (a teaspoonful frequently) will relieve nausea or weakness. Strong broths or milk alternately or mixed together (1 or more ounces every 2 hours) should be given when prostration exists. Robinson (*Med. Rec.*, Mar. 22, 1913).

The only death in 71 laparotomies was in a case of appendicitis in which a saline purgative had been given the woman behind the attending physician's back. Peritonitis followed, in spite of the prompt operation. E. R. de Aragon (*Rev. Med. Cub.*, July 1918).

A method which has had a considerable number of adherents for cases

that cannot be treated by operation owing to the circumstances above mentioned is that of the late A. J. Ochsner (**Ochsner method**).

In this method the measures advocated are as follows: (1) **No food or cathartics by the mouth**; (2) **lavage** if nausea and vomiting occur; (3) **nutrient enemata**; (4) **water by the rectum**.

After the patient is free from pain and normal four days, fluids are gradually given by the mouth.

All cases, however, are operated on admission unless the condition is very bad and inflammation has extended beyond the appendix. The **starvation treatment** above outlined is then continued until operation would be safe or until a circumscribed abscess forms which can be opened.

Of 30 replies received to a questionnaire addressed to Pennsylvania surgeons, regarding the treatment of peritonitis following ruptured appendix, 12 approved of the **Ochsner treatment** while 9 of the other 18 opposed to its general use reserved it for cases practically moribund when first seen. The writer himself reserves it for cases with rapid pulse, extreme distention and cyanosis, of which a few may thus be saved by temporizing; when such cases show subsidence and localization, however, with slower pulse and general improvement, he operates. A. F. Hardt (*Atlantic Med. Jour.*, Apr., 1924).

In addition to this may be used the **Murphy method of proctoclysis** in cases of appendicitis with peritonitis, with and without operation. In this procedure the fluid—warm **saline solution** [5j (4 Gm.) of **sodium chloride** and 5j (4 Gm.) of **calcium chloride** to each pint of water] at a temperature of 100° F.—is allowed to slowly drip into the rectum and be absorbed. The appa-

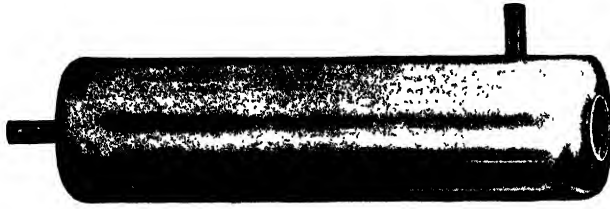


Fig. 1.—(One-third size). Represents a metal heating chamber, block-tin lined, with opening for electric heating unit and rubber-tube connections for intake and outlet of saline solution.



Fig. 2.—(One-third size.) Electric heating unit with socket connection and ten feet of cord. This unit can be used with either alternating or direct current 105 to 128 volts. See Fig. 8.



Fig. 3.—(One-third size.) Heat unit for alcohol or Bunsen burner flame with regulating piston. For use where electric current is not available. See Fig. 9.

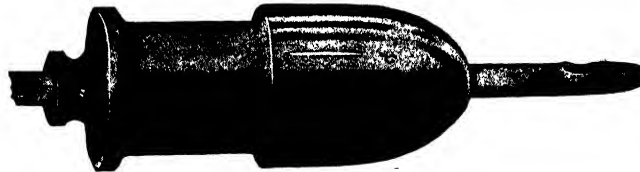


Fig. 4.—(One-half size of largest rectal tips.) Self-retaining rectal tips on catheter showing how adjustment can be accomplished by merely drawing catheter through to desired length.



Fig. 5.—(One-half size.) Pinch cock used entirely to close flow or for drop method

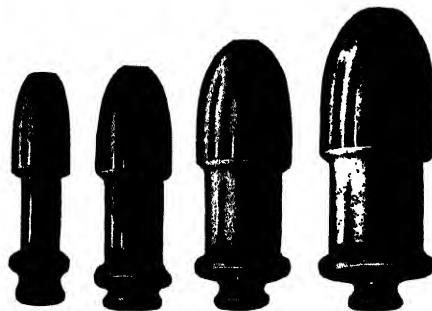


Fig. 6.—(One-third size.) Self-retaining rectal tips made in four sizes of hard rubber with opening through center to admit a soft-rubber rectal catheter, American size, No. 15. See Fig. 4.

ratus should be so arranged that about 18 pints (540 c.c.) are consumed in twenty-four hours. The fluid may be kept at an even temperature by an ingenious apparatus shown in the annexed illustrations.

The tank, however, should be about 6 inches above the buttocks. This is to be continued three days, and the patient should be in the position advocated by Fowler—on the back, with the knees

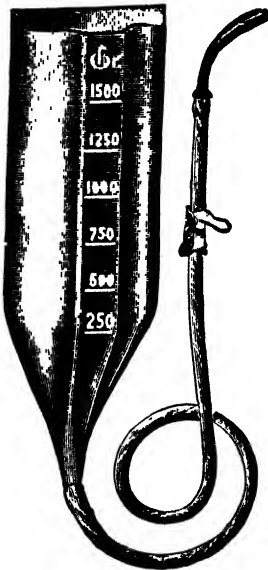


Fig. 7—Proctoclysis apparatus consisting of fountain syringe, large rubber tube and vaginal hard-rubber or glass tip. (*Murphy.*) (Journal of the American Medical Association.)

raised and the head of the bed elevated about 12 to 16 inches. The patient may be allowed to rest and the fluid stopped for an hour two or three times in the twenty-four hours.

This treatment, however, is apt to lead to dangerous complications if not preceded by operation. As a postoperative measure it is of great value.

A number of years ago the writer published the following conclusions after careful testing for a period of eight years. This form of treatment has been used by himself and many

others in thousands of cases with extra-appendicular infection, with the result of reducing the mortality in this most fatal form of appendicitis to less than 2 per cent., by changing an extremely dangerous acute into a comparatively safe interval condition:—

1. Patients suffering from chronic recurrent appendicitis should be operated on during the interval.

2. Patients suffering from acute appendicitis should be operated on as soon as the diagnosis is made, provided they come under treatment while the infectious material is still confined to the appendix, if a competent surgeon is available.

3. Aside from insuring a low mortality, this will prevent all serious complications.

4. In all cases of acute appendicitis, without regard to the treatment contemplated, the administration of food and cathartics by mouth should be absolutely prohibited and large enemata should never be given.

5. In case of nausea or vomiting, or gaseous distention of the abdomen, **gastric lavage** should be employed.

6. In cases coming under treatment after the infection has extended beyond the tissues of the appendix, especially in the presence of incipient diffuse peritonitis, conclusions 4 and 5 should always be employed until the patient's condition makes operative interference safe.

7. In case no operation is performed neither nourishment nor cathartics should be given by mouth until the patient has been free from pain and otherwise normal for at least four days.

8. During the beginning of this treatment not even water should be given by mouth, the **thirst being quenched by rinsing the mouth with cold water** and by the use of **small enemata** and by **chewing wax or paraffin**. Later, **small sips of very hot water** frequently repeated may be allowed, and still later **sips of cold water**. There is danger in giving water too freely, and there is great danger in the use of large enemata.

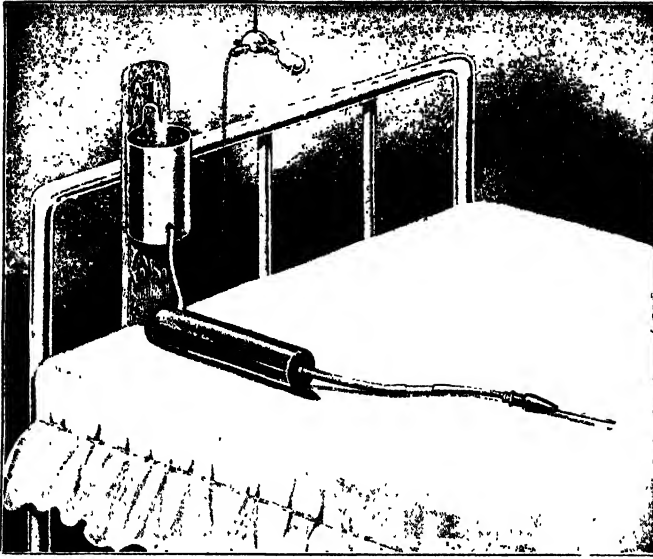


Fig. 8.—Electric heater in operation, showing it properly connected. A short glass tube connects catheter to rubber tubing.

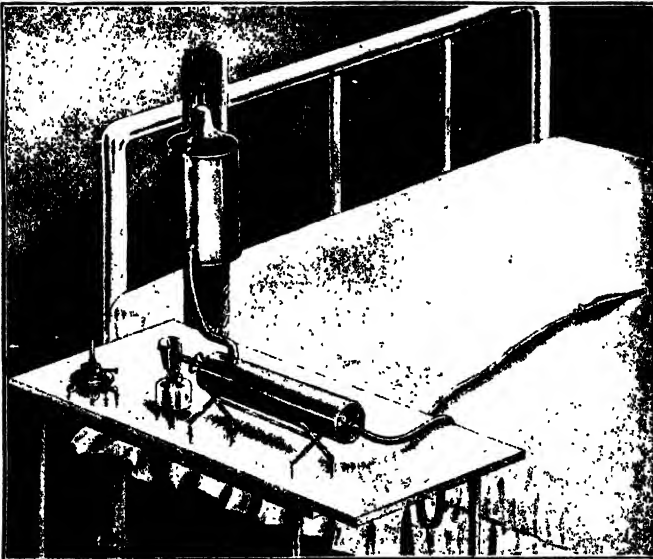


Fig. 9.—Alcohol or gas heater in operation, showing it properly connected. A short glass tube connects catheter to rubber tubing.

Proctoclysis apparatus ready for use. (*Murphy.*)  
(*Journal of the American Medical Association.*)

9. All of these cases are greatly benefited by the use of continuous **normal salt solution** by rectum given by the very slow drop method according to Murphy's directions.

10. All practitioners of medicine and surgery, as well as the general public, should be impressed with the importance of prohibiting the use of cathartics and food by mouth, as well as the use of large enemata, in cases suffering from acute appendicitis or peritonitis.

11. It should be constantly borne in mind that even the slightest amount of liquid food of any kind by mouth may give rise to dangerous peristalsis and may change a harmless circumscribed into a dangerous diffuse peritonitis.

12. The most convenient form of **rectal feeding** consists in the use of 1 ounce (30 c.c.) of any of the various concentrated liquid predigested foods in the market, dissolved in 3 ounces (90 c.c.) of warm normal salt solution, introduced slowly through a soft catheter, inserted into the rectum a distance of two or three inches.

13. This form of treatment cannot supplant the operative treatment of acute appendicitis, but it can and should be used to reduce the mortality by changing the class of cases with spreading peritonitis, in which the mortality is very high, into chronic appendicitis, in which it is very low after operation.

14. It is important to bear in mind the fact that this treatment is always indicated in every case of acute appendicitis without regard to whether an immediate operation is or is not contemplated.

15. It is further important not to be deceived by the very rapid improvement of what appear to be serious cases after introducing this treatment into the belief that the case is not a gangrenous or perforative appendicitis, because such patients may easily be killed by giving food too early.

For a number of years the writer has placed all these patients in the

**Fowler position** and has applied large **hot fomentations of saturated solution of boric acid**, held in place by an abdominal binder. Over this is placed an electric light in the form of a so-called **therapeutic lamp**. These methods seem to add to the comfort of the patient.

In severe acute cases the infection usually extends beyond the appendix after 48 hours, and practically always if the patient comes under treatment later than 72 hours after the onset. Almost all fatal cases following operation for acute appendicitis occur in patients who have been ill longer than 2 days and less than 10 days before operation. The writer by no means opposes all operative treatment of acute appendicitis, as some have thought; he insists upon an early diagnosis and immediate operation in all patients seen early enough to make it fairly certain that the infection is still confined to the appendix. Where neither food nor cathartics are given from the onset, and **gastric lavage** is used, the mortality is extremely low. In cases that have received food and cathartics at first and are consequently suffering from beginning diffuse peritonitis the mortality will be less than 2 per cent. if the peristalsis is inhibited by gastric lavage and interdiction of food and cathartics by the mouth. In this manner very dangerous cases of acute appendicitis may be changed into relatively harmless ones of chronic appendicitis. A. J. Ochsner (Therap. Gaz., Feb., 1921).

Discussing the postoperative mortality of appendicitis in *children* the writer urges operation at the earliest possible moment after the onset of the attack, preferably during the first 24 hours, while the infection is confined within the appendix. Where it has spread beyond, and a localized abscess is formed, the alternatives are immediate operation or delay until the second week, when there is considerable immunity to blood infection. Appendix abscesses very rarely burst into the peritoneal cavity if the patient is kept at rest in bed, on a

scanty and easily absorbed diet, and no aperients are given. During the second week the abscess may be opened and drained with the minimum of danger. If it is decided to operate at once during the dangerous period, it is essential that nothing but the introduction of a drainage tube into the abscess cavity be attempted. H. M. Brown (Lancet, Jan. 15, 1921).

Operation favored in any suspected case, regardless of the stage. The author also advocates early interval operations—between 7 and 12 days after the acute attack. Bastianelli (Policlin., Oct. 15, 1922).

All cases of acute appendicitis should be operated on immediately if a band of hyperesthesia is still present. Under appropriate treatment the majority of remaining cases subside and the appendix may be removed 7 to 10 days after the temperature and pulse have become normal. As compared with emergency operations this line of treatment shows a lower mortality, fewer complications, and a shorter stay in the hospital. In cases where expectant treatment fails, 24 hours' delay does not appear to influence the prognosis adversely. These conclusions are based on a series of 1503 cases of acute appendicitis admitted to the London Hospital. R. J. McN. Love (Brit. Jour. of Surg., Apr., 1923).

The writer favors immediate operation in all cases if conditions are proper, except for the few cases not seen until the 3d to the 8th day and which are judged inoperable because of extremely bad condition, extension of peritonitis to the diaphragm, etc., in which cases he favors **Ochsner's starvation treatment**. The latter cannot be carried out satisfactorily, however, without a trained nurse, and should be given in a hospital if possible. R. C. Dugan (Jour. Kans. Med. Soc., Jan., 1924).

Twenty-one successful appendectomies in the acute stage, bringing Bastianelli's series to 260 such cases (including some grave ones), in which the mortality was 2.23 per cent. Gucci (Policlin., Mar. 1, 1926).

The keynote of treatment is operative procedure at the earliest possible moment. In stout adults I do not believe the Ochsner treatment is indicated, except in the presence of very strong contraindication to operation.

For the pain, the suspended **ice-bag**, or frequently changed **cloths wet in ice water**, may be applied over the cecal region. If this is done frequently enough the pain can be kept in abeyance.

There is no treatment of appendicitis other than immediate operation, irrespective of the stage. The writer condemns not only cathartics but also the ice-bag, chiefly on the ground that, by relieving pain, it keeps the patient from the surgeon until a late hour. J. W. Kennedy (Amer. Jour. of Surg., May, 1924).

Opium was at one time highly recommended, but it is now regarded by practically all clinicians as a dangerous remedy. It masks the symptoms, and thereby tends to compromise the chances of operative procedures through delay; it locks the intestines and thereby prevents the expulsion of infectious discharges.

Report of 1000 cases of **appendectomy** in the quiet period after 1 or more attacks of appendicitis. The state of the appendix was: Apparently normal, 7; hypertrophy, 1; obliterative inflammation, 16; catarrhal, 511; stricture, 317; after abscess, 145; tubercle, 2; carcinoma, 1. There were 2 deaths, one from accidental infection of the peritoneum by the *Micrococcus pyogenes aureus*, and the other the result of vomiting and giving way of sutures in a stout woman of 56. W. H. Battle (Lancet, Feb. 12, 1921).

The general practitioner should refer his cases earlier to the surgeon. This would reduce the number of drainage cases, which later are nearly always followed by an incisional hernia. Some types of acute appendi-



*citis* ought to be operated on at once. Others are benefited by a rest of a few hours by instituting the Fowler-Murphy treatment. Children should be operated on at once. Behrend (Therap. Gaz., March, 1921).

*Bacillus Welchii* was observed by the writer to be the probable cause of death in a certain proportion of cases of gangrenous appendicitis. The germ has been found by Simonds in 90 per cent. of normal appendices removed at autopsy and by the writer in 90 per cent. of appendices removed at operation, whether acutely inflamed or not. It is an anaerobic germ which produces gangrene in simple or mixed infection. A serum is available for infection by this germ (also known as *B. aerogenes capsulatus* and *B. perfringens*), viz., the **perfringens serum** of Bull and Pritchett. In a number of desperately ill cases, after operation, administration of this serum appeared to give excellent results. The diagnosis of *B. Welchii* infection can be made in 2 hours by injecting suspected material into the liver of a guinea-pig, killing the animal after 3 minutes, placing it in the incubator, and examining its liver at the end of 2 hours. Sometimes even a smear showing typical encapsulated bacilli is sufficient. If positive, 100 to 200 c.c. of serum should be given intravenously and repeated 12 to 24 hours later. J. E. Jennings (N. Y. Med. Jour., June 6, 1923).

Preoperative **vaccine** treatment in acute or chronic appendicitis advocated in cases in which an intradermal test shows sensitiveness to colon bacilli. The vaccine employed consists of a suspension of colon bacilli killed by heat or of an extract of the same germs. Positive responses range from a bright red area several centimeters across to more extensive bluish patches. After such responses vaccination is carried out until the test becomes negative. The special object of the vaccination is to obviate the severe after-results sometimes following even a simple appendectomy on account of lowered resistance of the

patient to the colon bacillus. De Nabias (Bull. Soc. nat. de chir., June 28, 1924).

Whenever the operation is performed over 48 hours after the onset, the writer gives concurrently with the operation 2 to 6 injections of Delbet's stock **vaccine**. In cases operated within 48 hours, 1 vaccine injection is given if the appendix is found distended with pus. In the late cases the vaccine permits of omitting or limiting drainage and tends to attenuate abscesses of the abdominal wall. E. Bressot (Paris méd., Apr. 12, 1924).

In severely ill patients the writers recommend preoperative intravenous injection of 800 to 1000 c.c. of **normal saline solution**, which greatly increases the safety of the operation. In operating, these observers avoid the use of gauze packs to wall off the appendiceal region, on the ground that these packs are traumatizing and extend the peritoneal infection. Post-operatively, they proceed as follows: Plenty of **fluid intravenously**, if water cannot be taken by the mouth; sufficient **morphine**; **starvation** until peritonitis has subsided; avoidance of cathartics; **gastric lavage** freely; frequent examination for secondary abscesses, and prompt **drainage**, if such develop. Their mortality in 262 cases was 7.2 per cent. W. D. Gatch and D. C. Durman (Ann. of Surg., June, 1924).

**SURGICAL TREATMENT.**—Operation is indicated when the diagnosis is made, unless the appendicitis be the result of some other acute disease, typhoid fever, for instance, or when a sufficiently competent surgeon cannot be obtained. Under the latter conditions the patient should be kept in bed and the bowels moved by **enemata**, and the pain kept down by **ice compresses** or the suspended **ice-bag**, as previously stated. Persistent vomiting should be met by **washing out the stomach** and **rectal feeding**. Otherwise, a **liquid diet** by the mouth is permissible.

An inflamed appendix should be removed immediately, no matter what day of the disease. Fever is by no means a constant symptom of a gangrenous appendix or localized peritonitis. Inversion of the appendiceal stump is opposed by the authors. In all pus cases immediate use of a stock mixed infection vaccine is urged. The **Fowler position** and **Murphy drip** are also used, and, if post-operative ileus is feared, injections of **eserine**. Secord and Coates (Can. Med. Assoc. Jour., vi, 421, 1916).

The diseased appendix may do serious harm to the pelvic organs in childhood and young girlhood if left to work out its own destiny in a state of chronic inflammation. In the acute stage, the appendix should be removed immediately to forestall, if possible, a secondary involvement of the adnexa. If pus is present, every effort should be made to drain the pelvis. It is feasible in certain cases to drain Douglas' pouch through the vagina. Excepting in cases of localized abscess, a median incision is advisable, in order that the pelvic organs may be inspected, and any abnormalities of position or plastic adherence remedied. Graves (Annals of Surg., Mar., 1921).

The only point concerning which there is much disagreement in the surgical treatment of acute suppurative appendicitis is whether operation is indicated from the 2d to the 5th day. Some rely on the Ochsner treatment, hoping to convert a spreading infection into a local walled-off abscess, to be opened later; but the patient's interests are always best served by immediate operation unless he is moribund or the condition is already so much improved at the time of diagnosis that recovery without operation is assured. He always makes a right rectus incision, unless there is a definite abscess with unquestionable adhesions to the abdominal wall. Moist gauze is then used to wall off the diseased area, adhesions are gently separated, and the appendix is located. If it cannot at once be found,

or is removable only with great difficulty, it should be let alone. A drain should be properly placed and the abdomen closed about the drain. Anesthesia should be kept deep enough to avoid straining. A rather large split rubber drainage tube is introduced at the base of the cecum; another deeply into the pelvis, and a third, if required, upward toward the right kidney. To keep the patient quiet and reduce peristalsis **morphine** should be given after the operation. The patient's **bed** should be **warm**, with the **head elevated**. Administration of 10 per cent. **glucose solution** by Murphy proctoclysis should be begun at once. T. J. Brothers (Internat. Jour. of Surg., Jan., 1923).

Previous to operating for appendicitis the writer keeps the patient in the **Fowler position** and cleanses the bowel with a **low soapsuds enema**. The Fowler position is maintained while the patient is being transported to the operating room, during the operation, and through the convalescence. In a series of 80 cases treated between 1898 and 1915 the mortality from appendicitis with peritonitis was found to have been reduced 55 per cent. When postural drainage was not employed it was 81 per cent. and when it was employed, 46 per cent. H. Fowler (Med. Times, Feb., 1923).

When the operation can be resorted to, the following are its various steps:—

The *incision* that is generally preferred when there is no infection beyond the appendix proper is that recommended by **McBurney** (see *b*, colored plate). It crosses an imaginary line (*a*) drawn from the anterior superior spine of the ilium (*D*) to the umbilicus (*A*) at the juncture of its middle and lower thirds, and thus overlying the diseased structures. The integument and aponeurotic structures are alone to be incised, the muscular fibers being separated by means of the scalpel handle in a line parallel to their

course. As a result, muscular action will rather tend to approximate than to draw apart the edges of the wound and thus prevent postoperative hernia: a condition frequently met with, especially when the median incision was generally used. The latter is still resorted to by some surgeons, and is especially useful when diffuse abscess is present.

**McBurney's gridiron incision** has been considered as ideal for a large majority of the interval operations. If more room is needed the incision may be enlarged, the so-called extended McBurney incision. In nearly every case of appendicitis, it is best to enter the free abdominal cavity beyond the appendix and the inflammatory mass in order to examine for secondary abscesses and to determine the condition of the rest of the abdomen. If the appendix mass extends beyond the semilunar line it is better to open the abdomen by a vertical incision through the rectus sheath and separate the rectus muscle or to retract it. If it extends to the middle line or beyond, the opening should be in the middle line.

Wyeth gave preference to the **Deaver incision** because it offers free access to the cecum and appendix, and when, as is not infrequent, it becomes necessary to have more room for safe and thorough work, it can be extended indefinitely upward or downward, giving complete command of the peritoneal cavity with the minimum of risk of being followed by ventral hernia.

The **pararectal incision** is preferred by the writer. If the appendix is retrocecal, he adds an incision higher up and posteriorly, along the crest of the ilium and  $\frac{1}{2}$  inch from it. One can separate the external oblique and cut the internal oblique near the crest of the ilium without injury to the

ilioinguinal and iliohypogastric nerves, and by retracting the muscles inward, enter the abdominal cavity. Through this incision the regions high up in the abdomen, and even beneath the liver, can be made accessible to the surgeon's eye. Willy Meyer (Med. Rec., Apr. 23, 1921).

The writer takes a point from  $1\frac{1}{2}$  to 2 inches perpendicularly below McBurney's point and makes a **transverse incision** 3 inches long with its center at that point. After first incising through the skin and subcutaneous tissues, he next incises the aponeurosis of the external oblique in the same direction. The internal oblique and transversalis are then separated, exposing the peritoneum. With this incision no nerves are cut, there is no traction of wound edges, there is free exposure and easy access and drainage, less tendency to hernia, the appendix in the majority of cases is more easily found, and there is less post-operative pain. W. J. Moore (Glasgow Med. Jour., Apr., 1923).

The frequency of postoperative hernia has caused surgeons to greatly reduce the length of incisions, and Morris has shown that an opening through the muscular tissues  $1\frac{1}{2}$  inches in length is sufficient in the majority of instances. McBurney found that even in his method the opening in the deeper layers of the abdominal wall need not be more than 2 inches in length. No rule, however, can be laid down to apply to all cases. A 1-inch incision will suffice in some cases and 3 inches will be needed in others. It makes little difference, since with proper closure of the wound a hernia almost never occurs at the present time.

In operations for acute appendicitis requiring drainage, the gridiron incision leaves a weakness in the abdominal wall. A figure-of-eight suture, to be tied later when the drainage is removed, can be used for the approximation of the cut edges of the

aponeurosis at the weak point. If a postoperative hernia is tending to increase, it should be closed with an edge to edge union to the aponeurosis, or a flap operation after the method of Mayo for umbilical hernia performed. Where operation for acute appendicitis fails to relieve general infection, the wound should be re-opened and free drainage established. Other measures are **continuous rectal injections of saline** and **subcutaneous injection of anticolon bacillus serum in the flanks**, beginning with 30 c.c., followed by 20 c.c. at the end of 24 hours, and then 10 to 20 c.c. every other day. C. DaC. Hoy (Ohio State Med. Jour., Apr., 1922).

In children the writer favors the McBurney incision; in adults, a considerable percentage of such incisions are followed in 1 to 2 years by inguinal hernia because of muscular relaxation at the internal ring. In adults, he greatly prefers a straight right median rectus incision, as it permits exploration and is readily enlarged. C. H. Mayo (Jour. Amer. Med. Assoc., Aug. 23, 1924).

McBurney recommended his method only for non-suppurative cases or those in which drainage was not required.

Some operators have found that when difficulties arise and the incision has to be enlarged, the necessarily constant and hard retraction is likely to injure the tissues and sometimes to cause suppuration. The position of the incision is also thought by some to render proper drainage difficult to obtain. Other incisions are, therefore, resorted to.

An incision that has met with favor, under these conditions, is the incision designated by a dotted line in the annexed colored plate (*d*) along the outer border of the rectus muscle, beginning slightly below the level of the umbilicus and extending downward, in a straight line, 2 or more inches,

according to the operative area desired.

This same incision, amplified by another, has been recommended by Jalaguier, which is especially applicable to cases occurring in slim children. It is thought to prevent postoperative hernia better than any other. The skin and the aponeurosis of the external oblique are incised at the outer border of the rectus (*d*), and the aponeurosis on the inner side of this incision is then dissected for some distance from the anterior sheath of the muscle, and drawn toward the median line, exposing the sheath. An incision (*e*) parallel to the first is then made in the latter sheath about  $\frac{1}{2}$  inch to the inside of the border of the rectus, exposing the muscle. When the operation is finished, the deeper incision is closed and the rectus, permitted to slip in place, acts as protecting covering. Deaver and many other surgeons have used the incision along the rectus alone; also in adults for all cases of appendectomy.

Modified incisions have also been proposed by other surgeons, including Elliott, Vischer, Willy Meyer, Fowler, Weir, Wood and Rockey.

The abdominal walls having been penetrated, the margins of the wound are then retracted by an assistant, unless the abscess has already reached the surface. The peritoneum is then divided freely, but with great care. Any pus is carefully sponged out.

The handling of the intestines, and even their exposure to the air, is one of the most potent causes of shock after abdominal operations. The use of gauze packings, even of the temporary variety, causes subsequent shock, and, by injuring the delicate serosa, determines the formation of postoperative

adhesions. To lessen this element of danger in **appendectomy**, the following method will be found valuable, according to Lilienthal:

Through a small incision made in the locality preferred by the operator, a gloved finger is inserted, locating the cecum; a portion of this viscus is withdrawn with dressing forceps, and landmarks followed in the usual way to locate the base of the appendix. During this procedure there will be a little unavoidable handling of intestine outside of the abdomen. Having exposed the base of the appendix, a ligature is passed through the mesentery, to be used subsequently for ligating the organ; the ends of this ligature are left long, and are tied together or held with a clamp. The exposed part of the appendix and all other intestines are now returned to the abdominal cavity. When traction upon the ligature is made the base of the appendix and *nothing more* is brought into the wound. In the majority of cases it will be found extremely simple to deliver the entire appendix even though a considerable number of adhesions should be encountered. The ligation of the mesenterium, the ablation of the appendix, and the treatment of the stump are carried out in the usual manner. During the procedure of freeing and removing the appendix, this organ and *nothing else* is in the field. It is useful in most interval cases and in the early stage of the acute forms.

Matted coils are *gently* separated, and intestinal prolapse and contact with diseased surfaces are prevented by carefully packing the cavity around the cecum with pads of sterile gauze, the ends remaining outside or being held by clamps. This should be done in such a manner that no infected tissue or fluid be in any

way brought in contact with the healthy peritoneum. The walls of the pus-cavity are then disinfected with a **bichloride solution** of 1:5000.

The cecum being now isolated, it is important also to remove the cause of the abscess or its contents without causing septic material to invade the general peritoneal cavity.

If the appendix is not readily found, the anterior longitudinal band of the cecum is taken as a guide and followed until the appendix is encountered—usually behind.

In the second stage of appendicitis, with a circumscribed abscess around the appendix, active surrounding inflammation, or early peritonitis, the operation should be a limited one, *viz.*, simple opening and relief of pus tension, with removal of the appendix if accessible and easily amputated. Hoy (Ohio State Med. Jour., Mar., 1922).

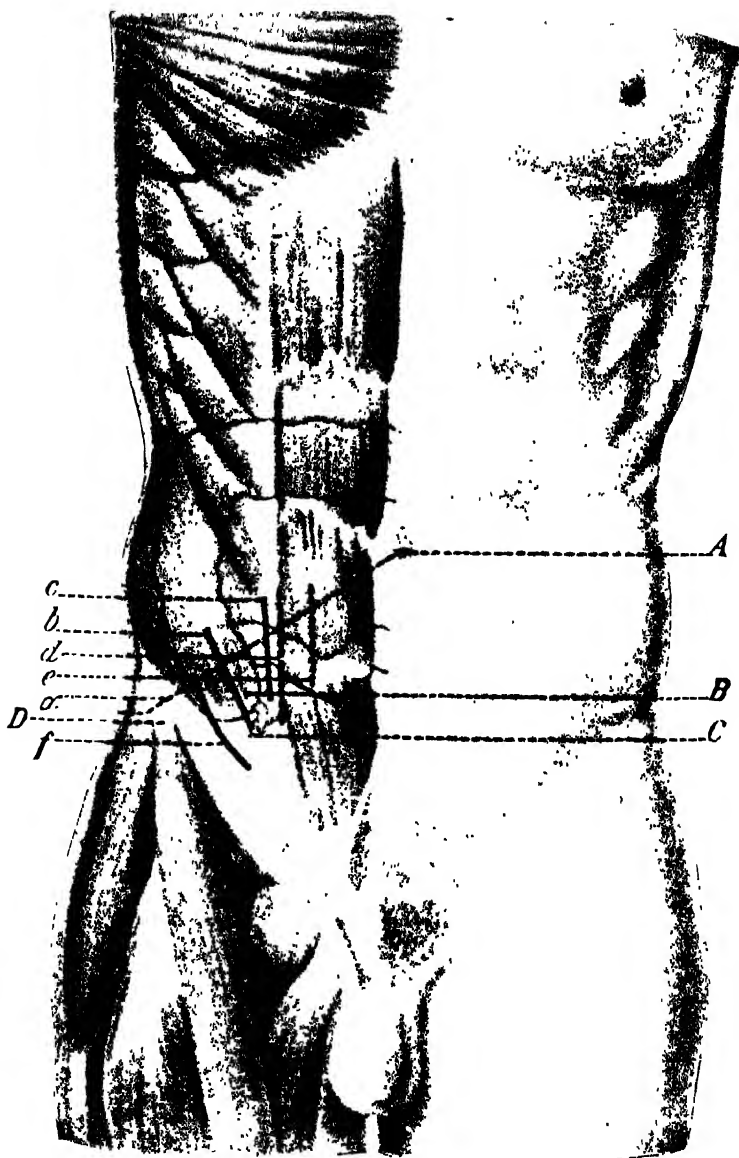
In the annexed colored plate only the tip of the appendix shows; but the greater part of the organ lies behind the cecum, its orifice in the latter being situated immediately under the spot where the McBurney incision (*b*) crosses the index line (*e*).

Adhesions are often encountered; care should be taken, when separating them, to protect the general peritoneal cavity with sterile gauze, as they are often septic.

The possibility of an anomalous conformation or position of the appendix should be borne in mind.

When located and brought out, the appendix should be clamped close to the cecum, cut off on the distal side of the clamp, closing the opening by means of a double row of Lembert (**silk**) sutures. The appendix is sometimes found detached and necrotic.

If there is a circumscribed abscess, it is poor surgery to insist, in every case



Incisions for Appendicitis.

*A*, umbilicus; *B*, cecum and termination of the ileum; *C*, vermiform appendix; *D*, anterior superior spine of the ilium; *b*, McBurney's incision; *d*, the Jalaguer-Deaver incision.



and at every period, upon finding and taking away the appendix in the face of all obstacles. In many cases of circumscribed abscess, and especially in those in which the appendix is bound down by adhesions in the depth of the wound, the surgeon should be content with evacuation, irrigation, drainage, and packing with plain gauze. Persistent search for the appendix and attempts at its removal in these cases are attended with such danger of opening the peritoneal cavity that they are not to be recommended.

Where an ice-bag had been applied before operation there was noticed a lack of effort on the part of nature to wall off the appendix. Where a **hot-water bag** or moist heat had been employed, a greater attempt toward walling off was manifest. Acute pain, stopping in 24 to 48 hours, with marked rigidity, suggests gangrene or acute stasis and is often followed in 12 to 24 hours by sudden pain indicating perforation. F. C. Warnshuis (*Lancet-Clinic*, Sept. 9, 1916).

In operating for suppurative appendicitis, the writers place the patient on his **right side** even before he has reacted, and keep him thus throughout convalescence, as long as drainage persists. **Rubber rings** for the hips and hollows contribute much to the patient's comfort. Bartron and Sherwood (*Journal-Lancet*, Jan. 1, 1922).

In cases with a definite mass in the right groin, caution is necessary in the incision down to the peritoneum. If the latter proves intact and movable over the mass, peeling it from the muscular parietes and seeking a low point of puncture are advantageous. With the finger, the operator next determines whether a true abscess exists or the mass consists merely of an enlarged appendix, wrapped in omentum and exudate. If no well-defined fluctuating abscess is palpable, through the intact peritoneum, the abdominal cavity should be entered and the appendix removed. If, on the other

hand, an abscess is felt, it may be punctured low with the gloved finger and safely drained through the space between the peritoneum and musculature. If the low puncture cannot be made without considerable risk of general peritoneal contamination, a **gauze tampon** and **drainage tube** introduced deeply alongside or under the abscess will induce spontaneous rupture with safe drainage in practically every case. In cases with difficulty in determining whether abscess exists, ample sero-purulent drainage has been attended by prompt disappearance of the mass and recovery. J. R. Eastman (*Jour. Ind. State Med. Assoc.*, Jan., 1923).

The stump is either simply disinfectected or the mucous membrane of the cut surface cauterized with **phenol** or the **cautery**. If the tissues about the base of the appendix are nearly normal, it is better to invert the stump and close it with two or three Lembert sutures. If not, a simple ligature on the proximal side of the clamp usually suffices.

Description of a simple, rapid procedure which deals effectively and safely with the stump of the excised appendix. The mesenterium is tied close to the appendix, but left sufficiently long after removal of the latter. A purse-string Lembert suture is passed through the cecal peritoneum around the base of the appendix, 1 centimeter from it. The appendix is grasped at its base with heavy forceps; 2 other forceps are placed just above and below the first, which is then removed and the appendix cut with a knife through the crushed portion. The stump is then whipped over with catgut suture. The hands having been cleansed, the purse-string suture is now pulled up as the stump is pushed into the lumen of the cecum. Finally the mesenterium is sutured to the cecum so that the suture, burying the appendix stump is buried and the cut edge of the mesenterium also covered. It is important that the first suture of the stump should roll into



the interior of the bowel when the stump is pushed into the cecum. Hemorrhage from the stump cannot occur, because it has been tied by this suture-ligature. Van Hook (Boston Med. and Surg. Jour., Apr. 12, 1923).

**Drainage** is usually maintained until healing is shown to be taking place from the bottom of the wound. Gauze is used, partly in order to stimulate the adhesions between coils of intestine which surround it and to shut off the general peritoneal cavity from the infected portion. A simple cigarette drain answers the purpose. It is important to withdraw the gauze plugs by rotary movement rather than by direct traction; it causes less pain.

In appendicitis with localized abscess or general peritonitis, after swabbing out as much as possible of the septic material, many surgeons now leave the peritoneum to deal with what remains, closing it without drainage. The abdominal wall, less resistant to infection, frequently suppurates and breaks down. An attempt should, however, be made to obtain primary union by disinfecting the wound after the peritoneum has been closed. For this purpose the writer found that 1:1000 flavine solution gave the best results, the incision healing by primary union in 6 out of 7 cases of suppurative appendicitis. For the first 24 hours physiologic salt solution should be given freely by **enteroclysis**. R. G. Riddell (Brit. Med. Jour., Feb. 24, 1923).

In appendiceal abscess in children the writer **drains toward the iliac crest** unless the mass points down toward the rectum, when **rectal drainage** can be instituted. The surgeon should not attempt too much. Often the abdominal wound is left wide open, especially if peritonitis is evident. In many cases a Mikulicz or modified Harris drain is used. Drainage for a long time is essential unless the drainage of pus ceases. The **Fowler position** and **maximum ingestion of fluids**

are essential in peritonitis. K. Speed (Amer. Jour. of Surg., May, 1923).

The customary procedure in operations for appendix peritonitis is departed from by the writer in that he closes the wound without drainage. The ruptured appendix is regularly removed. The incision is made large enough to permit dry mopping of the pelvis, thus removing several ounces or even a pint or 2 of pus; this, he finds, causes practically no irritation. Drains do not drain more than 24 hours and leave an entrance for new germs from the exterior. A case operated for diffuse peritonitis within 48 hours after the onset of pain and closed without drainage will, in all probability, get well. A local abscess, on the other hand, must always be drained, as the peritoneum has been destroyed and the remaining surface will continue to form pus. Buchanan (Atlantic Med. Jour., Apr., 1924).

The writer's procedures regarding drainage are these: (1) Operation within 24 hours after onset: Complete closure after removal of the appendix, even if turgescient and distended with pus. (2) Operation after 48 hours, in the presence of slight peritoneal reaction, edema of the meso, but no pus: Complete closure after removal of the appendix, whatever be its condition. (3) Walled-off abscess operated after 48 hours: (a) Appendix removed; drying with ether: Small drain in the lower end of the wound, removed after 3 or 4 days. (b) Appendix not removed: Drain in the lower end. (4) Diffuse peritonitis: (a) Appendix removed: Drain in the lower end. (b) Appendix not removed: Large drain in Douglas's cul-de-sac. E. Bressot (Paris méd., Apr. 12, 1924).

In acute cases with gangrene of the appendix but without diffuse peritonitis, the writer closes the peritoneum but refrains from tightening the sutures in the abdominal wall until, after 5 days, it is seen that no symptoms of peritonitis are developing. In late years none of his cases have died from peritonitis. Schönstadt (Med. Klin., Mar. 26, 1926).

**Remote Abscesses.**—While most abscesses are found in the appendicular region, there are other types of abscesses which may occupy areas quite remote from the latter, including, we have seen, the lungs.

To properly locate a remote abscess is of great importance. When its evacuation becomes necessary the selection of the best point for incision is in order. This subject is graphically portrayed in the annexed colored plate prepared from sketches and an interesting paper by Dr. M. L. Harris.

**Description of Colored Plate on the Location of Appendicular Abscesses.**—A circle of an inch and a half in diameter—the size of a silver dollar—drawn about the center of the posterior surface of the cecum will touch the base or point of origin of the appendix in about 96 per cent. of all cases. It will thus be seen how constant is the location of the base of the appendix. The average length of the adult appendix is 9 cm., or  $3\frac{1}{2}$  inches. A circle, then, of 4-inch radius drawn about the same center as the smaller circle will give a very large area in the abdominal cavity, anywhere within which the apex of the normal appendix may be found located. (See illustration.)

The space within the large circle (see illustration) may be subdivided into five separate areas (marked 1, 2, 3, 4, and 5), each having distinct and well-defined boundaries. The appendix may be found in any one of these areas, and, when an abscess forms about the inflamed organ, it is the particular area in which the appendix is located which gives the abscess or exudate its characteristic location and outline, which limits its extension in one direction and favors it in another, and which should guide us in the selection of the best point for incision.

**Area 1: Inframesenteric.**—The appendix is met with in this area in about 60 per cent. of the cases, either superficially situated, approaching anteriorly, or lying deeply on the posterior wall; it may extend directly inward, hugging the under surface of the mesentery at the ileum, or inward and downward, reaching often into the true pelvis. The mesentery above prevents the extension of

abscesses in an upward direction, but gives them a tendency to extend forward and to the left.

The pelvic abscesses are limited in the male anteriorly by the bladder, posteriorly by the rectum and pelvic wall, and above by the sigmoid and loops of small intestine. In the female they fill Douglas's *cul-de-sac* or occupy the ovarian region on one or both sides, where they are often with great difficulty differentiated from pelvic abscesses of tubal or ovarian origin. The danger of infecting the general cavity on opening these abscesses from above is very great, and the advisability of draining through the vagina in the female, as in other septic pelvic troubles, comes into serious consideration.

The interintestinal abscesses (see also illustrations) are usually situated near the median line, and are consequently best opened at this point. Adhesions may limit them, or there may be no adhesions and the free peritoneal cavity must be traversed to reach the abscess, after packing with iodoform gauze to prevent diffusion of pus. It is often impossible to prevent pus escaping into the general cavity, with a resulting fatal acute septic peritonitis. It is in those cases that the advisability of doing a *deux temps* operation should be considered. Should the appendix be found floating free in the abscess cavity it may be removed, but if it be firmly imbedded in the exudate forming part of the abscess wall it should, under no circumstances, be torn out and removed, if by so doing we endanger breaking into the general cavity, thus leading to general sepsis.

The exudate may also come to the surface, forming adhesions to the anterior abdominal wall, just internal to the cecum. (See illustration.) The abscess is limited externally by the cecum and internally by the loop of ileum which almost always covers over the end of the cecum and the omentum. It is usually best opened by a vertical incision over the inner border of the cecum. Care should be taken not to separate the loop of intestine internally, particularly at its lower angle, as pus then escapes at once into the pelvis.

The appendix can nearly always be removed, as it usually lies posteriorly or anteriorly, and it can be done without disturbing the internal wall of exudate which protects the general cavity.

*Area 2: Retrocecal.*—Abscess is met in this area (see also illustration) in about 23 per cent. of the cases. The appendix lies in the little pouch posterior to the cecum, more or less curved or folded upon itself or extending downward and outward to a more or less marked degree.

It is best opened by an oblique incision parallel to the outer half of Poupart's ligament, coming down upon the outer border of the cecum, which should be raised up and turned inward. The appendix can nearly always be removed, unless it should be too firmly imbedded in the exudate forming the inner wall.

*Area 3: Supramesenteric.*—Abscesses here (see also illustration) have a tendency to spread toward the liver and duodenum. The appendix lies above the mesentery of the ilium and internal to the inner layer of the mesocolon.

These abscesses are best reached by an incision along the external border of the right rectus muscle, great care being taken not to break down the adhesions between the loop of small intestine to the inner side. (See incision *c* in first colored plate.)

*Area 4: External.*—This is the space between the outer border of the colon, with its outer layer of mesocolon, and the external abdominal wall. The appendix may extend upward and outward into this space, its tip sometimes reaching nearly to the under surface of the liver. Abscesses spread to the liver and have repeatedly ruptured into the pleura and even into the bronchi. (See illustration.)

They may be reached by an oblique incision extending from above the crest of the ilium downward and inward, parallel to the outer third of Poupart's ligament, or, if the abscess is high up, by a longitudinal incision over its most prominent part, care being taken to not injure the iliohypogastric nerve. The appendix can nearly always be removed, as there is no danger, in separating the adhesions about it, of opening the general cavity.

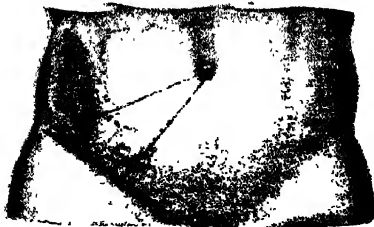
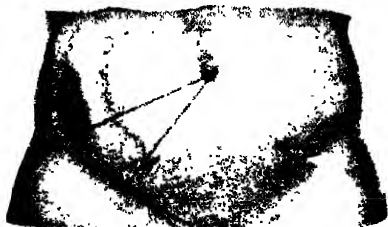
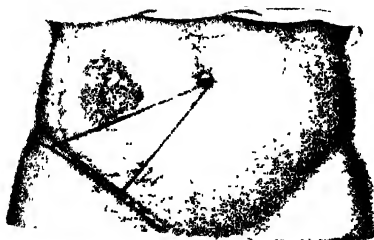
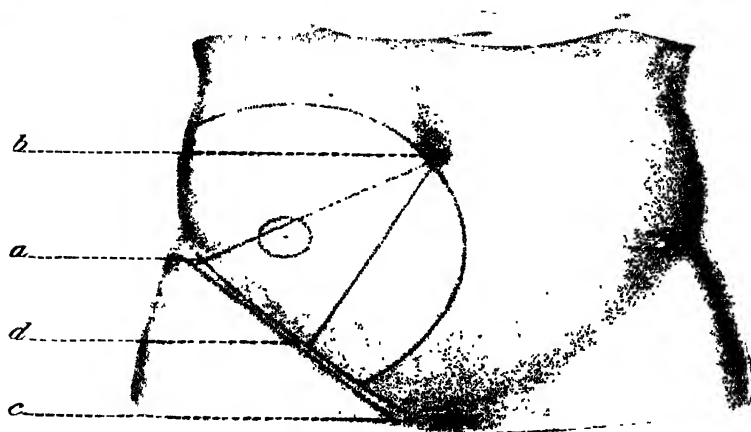
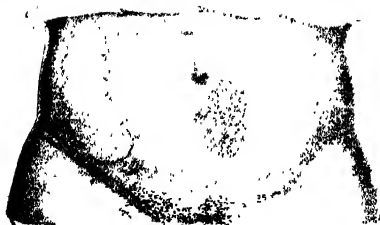
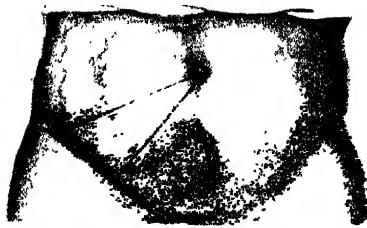
*Area 5: Retrocolonic, or Extraperitoneal.*—In the cellular space posterior to the colon between the two layers of the mesocolon. (See illustration.) Abscesses here are entirely extraperitoneal. The colon is pushed forward.

*Subphrenic Abscess.*—This complication of appendicitis was thought at one time to be quite rare, but recent developments have shown that this was due to the fact that they were seldom diagnosed. As stated by Christian and Lehr, they may occur in one of four ways: As a localized abscess, a part of general purulent peritonitis; by extension of the diseased process from the appendix to the subphrenic region by an intraperitoneal route; by extension of the diseased process by an extraperitoneal route, either by way of the lymphatics or by infiltration through the retroperitoneal tissue; by way of the blood-current as part of a general embolic septic process, or as a sequence of liver abscesses which are of the portal vein.

Several modes of onset are characteristic according to Elsberg who bases his study on 179 cases collected by Maydl:

(a) A few days after the acute symptoms of appendicitis have been relieved and the temperature has fallen to the normal, the patients begin to complain of pain in the lower part of the right chest, the temperature begins to rise, the area of liver dullness is found to be somewhat enlarged, there are friction sounds over the hepatic region, and tenderness in one or two intercostal spaces. There may be slight or well-marked jaundice. Within a few days the pain over the liver becomes less, while the signs of fluid become evident.

(b) Before the acute symptoms of appendicitis have entirely subsided, although the local symptoms are much improved, the daily temperatures begin to take on a remittent type, and the patients begin to lose flesh and strength rapidly. These patients look very ill from the beginning. They do not com-



Location of Appendicular Abscesses. (*M. L. Harris.*)

*a*, anterior superior spine of the ilium; *b*, umbilicus; *c*, symphysis; *d*, Poupart's ligament



plain of much pain, although they may have tenderness in the lumbar region; the most marked symptom is the rapid loss of flesh and strength. No further physical signs may be discoverable until the bulging of the abscess in the lumbar region is found.

(c) After having recovered from the attack of appendicitis in a satisfactory manner, some of the patients never regain their former health. Without any change in the temperature, respiration, or pulse, the patients complain of continual slight pain in the right chest. The pain persists for weeks or months; physical examination and aspiration of the right chest result negatively. The patients never look very ill. After a varying length of time, the presence of fluid under the diaphragm, and perhaps also in the pleural cavity, is discovered by means of physical examination and the aspirating needle.

As noted by Eisendrath, there are 5 methods of draining a subphrenic abscess: (a) By an incision in the epigastrium; (b) by an incision along the costal arch; (c) by an incision in the lumbar region; (d) by the transpleural route; (e) by pushing the pleural reflection upward and opening the abscess cavity through an incision in the diaphragm without opening the pleural cavity. The first 3 methods are indicated when there is bulging in the corresponding regions. If suppuration continues and septic symptoms reappear, either an accompanying empyema, insufficient drainage, or persistence of the original focus is indicated.—EDITORS.

Subhepatic abscess, *i.e.*, abscess in the subhepatic fossa or Morison's pouch, below the right lobe of the liver, in front of the kidney and above the hepatic flexure, should be distinguished from subphrenic abscess. A patient operated upon for appendicitis with peritonitis, after improving for one or two weeks, manifests afternoon fever and polymorphonuclear leucocytosis. Sooner or

later, deep tenderness is elicited in the right upper quadrant just at or below the liver edge. A mass is finally detected deep in the subhepatic area, with tenderness in the 10th and 11th right interspaces and in the costovertebral angle. The mass may be ballotable into the loin, and suppuration of or about the kidney will be suspected. As a rule, surgical drainage is indicated, through the loin, by an incision corresponding to the anterior part of the usual kidney incision. The prognosis is good if the lesion is recognized early and drained. P. W. Aschner (N. Y. Med. Jour., June 6, 1923).

*Diffuse Abscess.*—If an abscess has opened into the peritoneal cavity or the appendix has ruptured into the free peritoneal cavity, causing diffused septic peritonitis, a good-sized incision is made parallel to the border of Poupart's ligament or the ordinary McBurney incision may be made, the peritoneal cavity is opened, and the contained fluids are gently withdrawn. The appendix is removed; further collections of fluid are looked for and withdrawn with a sponge on a handle. The cavity is washed out with a **saline solution**, and drainage is provided for by a glass tube, or rubber tubes threaded with a capillary gauze drain. The wound is left open or closed at the ends by a few sutures. **Nutrition by rectum** is kept up for a day or two, and the deep packing is not disturbed for four days.

### CHRONIC (RELAPSING, OR RECURRENT) APPENDICITIS.

**SYMPTOMS.**—The symptoms of an exacerbation of appendicitis—for a relapse is practically such—are the same as in the acute form, except that they are apt to be more severe and early perforation is liable to occur. The simple catarrhal form may be suspected when the recurrences (hence, *recurrent appen-*

*ditis*) happen more than four or five times, and last not more than a week, though no tumor is felt. Discomfort in the region of the appendix between the attacks is complained of, and the appendiceal area is somewhat sensitive to pressure, and sometimes the seat of actual pain with slight fever. The attacks may be slight at first and continue to be so, but a severe and even fatal attack may occur at any time. Hence, the advisability of resorting to appendectomy during an interval. Fatigue, muscular strain, dietetic errors, etc., may bring on an attack.

An attack is usually ushered in by severe abdominal pain, sometimes beginning in the epigastrium or mid-abdomen, often with nausea and vomiting. The pain then centers itself, if it has not done so from the start, in the appendiceal region. Flatulence and a feeling of distention and diarrhea are also present in most cases.

In 103 operative cases of chronic appendicitis the most constant symptoms were pain and tenderness, present in 95 cases, and nausea, 89 cases. Constipation was present in 80 per cent. of the cases, alternating at times with diarrhea or normal stools. There were also flatulence, tenesmus, anorexia, epigastric fullness, eructations and heartburn. Fatigue of the right leg in walking was sometimes noted. There were bladder disturbances in 6 cases, and slight loss of weight and weakness in 25 per cent. The objective symptoms comprised: Tenderness, 85 per cent.; muscular rigidity, 70 per cent.; cutaneous hyperesthesia, 38 per cent., and cecal enlargement, 60 per cent. The general clinical picture is diagnostically significant. C. ten Horn (*Beitr. z. klin. Chir.*, No. 2, 1921).

There are instances of disease of the appendix which, perhaps for toxic reasons, cause from slight bleedings to intermittent frank hemorrhages from the gastric mucosa; this condi-

tion requires appendectomy for its permanent and complete cure. Basler (*Jour. Amer. Med. Assoc.*, July 2, 1921).

In children, chronic appendicitis is a grave disorder. It begins with pain in the umbilical region and symptoms of indigestion with, in some instances, gastric pain. Such children are periodically indisposed and suffer from headaches, anorexia, fatigue, irritability, and look wan or even haggard. McBurney's point may not be sensitive and the temperature may be subnormal. Lunckenhein (*Munch. med. Woch.*, Jan. 6, 1922).

Stress laid on **Bastedo's sign** as the most important indication of chronic appendicitis. As the inflation of the colon with air progresses, the patient feels pain over the right iliac fossa, whereas the normal subject feels only a diffuse discomfort. A negative test does not definitely exclude the disease, but very positive other evidence must then exist to make the diagnosis. Tenderness is usually found over the distended appendix. A. F. Hurst (*Guy's Hosp. Reports*, Oct., 1922).

The following objective findings are of diagnostic importance:

- (1) Tenderness in ileocecal region.
- (2) Rigidity over the right rectus, sometimes present, especially if there are pericecal adhesions.
- (3) Gastric hyperacidity, less often subacidity.
- (4) *Aaron's sign*: Pressure in the appendicular region causing epigastric pain.
- (5) *Bastedo's sign*: Ileocecal tenderness on colon inflation, present in a few cases, chiefly with adhesions.
- (6) Tenderness over the appendix region on giving an enema (rare).
- (7) *Reder's sign*: Tenderness upon rectal examination (very rare).
- (8) *Rovsing's sign*: Pain over the appendix region upon pressure on the left side at a point corresponding to McBurney's on the right. Held (*Amer. Jour. Med. Sci.*, June, 1924).

The general health and nutrition are usually impaired in these cases, partic-

ularly if the intervals between the attacks grow shorter. More or less marked neurasthenia, with coldness of the extremities, irritability, moroseness, and mental apathy, is usually present, owing, doubtless, to the anxiety which the disorder inspires. Stubborn constipation, more or less headache and vertigo, anorexia, a disagreeable "bilious" taste in the mouth, and "bad breath" are commonly complained of, the tongue, especially at its base, being often thickly furred. A peculiar pasty or bloated appearance of the face is also noticeable in some cases.

Appendiceal dyspepsia, previously referred to, and due, according to Moynihan, to exaggerated activity of the pylorus, is aggravated by gastrointestinal autointoxication through the intermediary of the appendiceal disorder, and disappears after appendectomy.

All the symptoms of the vagotonic state may occur in chronic appendicitis, *viz.*, nausea, vertigo, vomiting, constipation, spasm of the pylorus with hypersecretion, asthma, sensitiveness to cold, frequent urination, pallor of the lower half of the face, slow pulse, and low blood-pressure. This vagotonic condition is possibly the result of toxic irritation of nerve-fibers in the appendix. Neuromas have been found in the chronically diseased appendix. Some of the vagotonic symptoms, *e.g.*, asthma, can be relieved at once by operation. E. Enriquez, R. A. Gutmann and E. Rouvière (Bull. Soc. méd. des hôp., Dec. 22, 1921).

The epigastric discomfort in chronic appendicitis is irregular in time of onset. Upper abdominal pain is usually worse after exertion, and pain in most cases appears soon after ingestion of food. Capriciousness in intensity of the pain and its radiation toward or about the umbilicus or lower abdomen, tenderness over McBurney's point and periclicity of attacks are all characteristic. Vomiting is less frequent than in ulcer and does

not afford as great relief; loss of appetite and weight often helps in the distinction. Duodenal ulcer may be excluded with the X-rays. The diagnosis of chronic appendicitis must be reached largely by exclusion. F. B. Gurd (Canad. Med. Assoc. Jour., Apr., 1923).

After the age of 4 years chronic appendicitis is a not infrequent sequela of eruptive diseases and acute infections. Cyclic vomiting never recurred among the writer's cases in which appendectomy was carried out. In children between the ages of 6 and 8 years severe dyspepsia is usually dependent upon chronic appendicitis. Excellent results follow appendectomy. J. M. Maidagán (Rev. méd. del Rosario, Apr., 1923).

In hypochondriacs and hysterical subjects both acute and chronic appendicitis are sometimes suggested by symptoms recalling the latter condition, the hyperesthesia and pain in the right iliac fossa being especially marked. But a careful study of the history and antecedents of such cases, absence of tenderness when the patient's attention is attracted elsewhere, and of the doughy mass in the region of the appendix usually serve to indicate the true nature of the case.

To facilitate the diagnosis of chronic appendicitis the writer tries to *ascertain the lower, outer and inner borders of the cecum*, usually distended with gas, by *percussion*; he estimates from this the position of the appendix, and finds out whether there is tenderness at that point. Where mapping out the cecum by percussion is not possible, he places the thumb at the junction of the right edge of the rectus muscle and umbilicospinal line, and, with it pointing toward the ensiform, sinks it in about halfway to the back of the abdominal cavity; next he swings it to the right of the patient at a right angle to the line of previous pressure, thus *pinching the appendix against unyielding structures*.



and eliciting tenderness if it be diseased. If this test is negative, he repeats it  $\frac{1}{2}$  inch lower, and tests again until the brim of the pelvis has been almost reached. Control is made by pressure on the left side. Bassler (Amer. Jour. Med. Sci., Aug., 1913).

Two signs belonging to the sympathetic and autonomic nervous system are of great importance in making a differential diagnosis between chronic appendicitis and other affections of the abdomen and pelvis. They do not occur in acute appendicitis. Chronic irritation of the appendix excites the second and third right sympathetic lumbar ganglia, the *fused ganglion*, rendering it hyperesthetic. Deep pressure upon the abdomen about  $1\frac{1}{2}$  inches to the right of the navel and a trifle below it evokes this hyperesthetic point. The second sign consists in permanent distention of the ascending colon. It is called the *cider barrel sign*. Percussion on the left side of the patient's abdomen gives a normal resonant note suggestive of such a barrel in October (full), while percussion on the right side of the patient's abdomen gives a note suggestive of the cider barrel in March. R. T. Morris (Med. Rec., Jan. 11, 1919).

Upon operation in cases in which pressure on McBurney's and Lanz's points causes abdominal pain, changes are often found, such as kinks or membranes, which interfere with the mobility of the appendix. In children who are pale and thin, do not do good work in school, have a poor appetite, and are often constipated, yet do not complain of anything except perhaps headache, examination frequently reveals a painful Lanz's point, with pain radiating outward from the point. In such children removal of the appendix does wonders. *Lanz's point* is at the inner third of the line connecting the 2 anterior superior spines, slightly inward from the outer border of the rectus muscle. V. E. Mertens (Wiener klin. Woch., Mar. 30, 1922).

The most important and constant sign of appendicitis is tenderness and

localized pain, but in recurrent appendicitis it is difficult to elicit the pain with the patient lying in the usual posture and by unimanual pressure. The following 4 procedures have been found useful by the writer to bring out the pain and its location: (1) With the patient in dorsal recumbency, a sudden backward thrust is made at the end of expiration by the examining fingers to the right of a line joining the umbilicus and ensiform cartilage. Usually no pain results, but a shock variously described as a pull, turn, twist, jar or knock is felt by the patient at the seat of the trouble. This sign is especially symptomatic of adhesions. (2) With the patient in the Sims position on the right side, with his back to the examiner, the tips or palmar surfaces of the fingers are pressed backward, systematically covering the ileocecal region until the painful spot is encountered. (3) With the patient lying on his back, the right thigh is supported at a right angle to the abdomen by the arm and elbow passed behind the thigh below the knee. This facilitates detection of any tenderness or rigidity of the cecum and appendix. (4) During a prolonged interval between an expiration and inspiration (relaxing the abdomen) bimanual pressure is applied with the fingers on opposite sides of the abdomen, preferably with the examiner between the patient's legs. This procedure may be combined with any of the preceding maneuvers. It is well to percuss out the limits of the cecum from the start. L. Drosin (N. Y. Med. Jour., June 6, 1923).

The ulcerative form with its attending danger of perforation may be suspected when a tumor is felt in the interval, and especially when the tumor has increased in size during the access.

The large majority of the attacks are due to any cause which may awaken the latent catarrhal process resulting from a previous attack treated medically. The pathological characters are the same as in the acute form, except in the fact that

adhesions are likely to be found if anything but a very mild attack has previously occurred.

In an analysis of 100 cases of obliterative chronic appendicitis operated upon by Deaver, the writer found that there are 3 types of symptoms: (1) *reflex*, due to irritation of the nervous mechanism of the appendix, the "dyspeptic" type of appendix; (2) *local*, due to mesenteric and peritoneal contraction and inflammatory bands or adhesions affecting the appendix, cecum, ileum, or ascending colon; (3) *consecutive* symptoms, general and local, consequent upon disturbed function of the ileocecal region. Simple appendectomy avails for reflex symptoms, but in local and consecutive symptoms only insofar as the operation permanently frees symptom-producing contractions, sclerosis, or adhesions. D. B. Pfeiffer (Annals of Surg., Apr., 1915).

Description of a clinical condition simulating the ordinary chronic abdominal syndromes, especially chronic appendicitis, and apparently due to stasis in the ascending colon with consequent low-grade infection and band formation at the point of lowest resistance of the bowel wall. Chronic appendicitis often accompanies the condition. The chief complaint is vague pain, usually in the right side of the abdomen, but not definitely limited to the right lower quadrant. It tends to spread to the right hypochondrium, and often radiates to the back. There is also a history of a feeling of heaviness after eating, anorexia, gaseous eructations, nausea and occasional vomiting. Constipation is the rule. Tenderness and rigidity are more diffuse and higher up than in chronic appendicitis. All of the patients led sedentary lives. An absolute diagnosis can be made only with the X-ray and barium meal, showing an altered contour of the secondary and transverse colon, with bands of adhesions passing over the ascending colon, involving to various degrees the transverse colon, and pro-

ducing partial or complete obstruction. The treatment consists in freeing the adhesive bands by careful dissection, peritonization of all raw surfaces, keeping the patients as constantly as possible on the left side for several days following operation, and frequent activation of the bowel with magnesium sulphate. The symptoms are quickly relieved by this operation, and no recurrence has followed. C. Davison, M. Davison and D. J. Royer (Surg., Gynec. and Obstet., Feb., 1924).

Chronic appendicitis in adults classified in 4 separate categories: One low grade infective and 3 non-infective, irritative lesions. The irritative lesions are in scarred remains of appendixes, appendixes undergoing fibroid involution, and cases of lymphoid hyperplasia. In children the lesions are largely confined to 2: One low grade infective and 1 irritative, the latter seen in children with the "lymphoid diathesis." The peritoneal sheath of the organ not yielding to the lymphoid hyperplasia within, there is pain, colic and disturbance of the abdominal sympathetics, with tenderness on deep pressure, not at McBurney's point, but at the site of the fused ganglia of the lumbar sympathetics, a little to the right of and below the umbilicus. R. T. Morris (Jour. Amer. Med. Assoc., Sept. 27, 1924).

Every case of latent appendicitis, in addition to conjunctival subicterus, shows the *phrenic sign*, viz., tenderness to gentle pressure over the right phrenic nerve with the finger tip low down in the neck. The sign is negative where the appendix is not diseased. When it is positive in gastric or duodenal ulcer, the ulcer is secondary to appendicitis. The sign becomes negative in 4 to 18 hours after appendectomy. It is due to an appendicular lymphangitis ascending about the structures in the subhepatic region and irritating the subhepatic terminals of the phrenic nerve. Ilescu (Bull. de l'Acad. de méd., Jan. 26, 1926).

Fluoroscopic examination with the aid of the barium meal facilitates the

diagnosis in a large proportion of cases.

Where the suspected appendix fills in part only, or empties before it has completely filled and the case is doubtful, the usual dose of barium should be divided and given in a succession of meals. By careful technique the appendix can be revealed and studied in more than 80 per cent. of all cases. The normal organ fills and empties at about the same time as the cecum. In young people it may fill and empty repeatedly, the cecum remaining full. The best views are secured 12 to 14 hours after the opaque meal. Spriggs and Marxer (*Lancet*, Jan. 18, 1919).

The direct X-ray signs in the appendix are tenderness, fixation, kinking, change in shape, abnormal position, lack of filling, slow emptying, beading, and adhesions in the ileocecal region. The indirect signs are pyloric spasm, gastric residues, and ileal stasis. Most of these are merely suggestive, and several are needed for a diagnosis, along with the clinical evidence. If there is tenderness and no fixation, the other signs count for little. If tenderness coincides strictly with the visualized appendix, it constitutes the best single sign of a pathologic condition. Delayed emptying of the appendix, *i.e.*, much over 36 hours or after the cecum has emptied, suggests poor drainage. Permanent fixation is important, especially if it involves one portion, the tip or median part, and causes kinking and deformity. Anomalous position is significant only if it is fixed. F. W. White (*Boston Med. and Surg. Jour.*, Apr. 19, 1923).

A valuable indication of chronic appendicitis is a failure of the opaque suspension to leave the appendix after 2 tablespoonfuls of castor oil have been taken to empty the bowel. The author also takes the patient's temperature in the rectum and the axilla after a walk. In appendicitis the difference between the 2 readings is often greater ( $0.8^{\circ}\text{C.}$ — $1.44^{\circ}\text{F.}$ ) than

normal. L. Kuttner (*Med. Klin.*, Apr. 20, 1924).

For visualization of the appendix in chronic appendicitis the writer advocates giving 0.001 Gm. ( $\frac{1}{55}$  grain) of atropine in an enema 1 hour after the barium meal. With this procedure visualization was obtained in 50 per cent. of 36 cases, as against 18 per cent. without the atropine. Bretton (*Médecine*, Sept., 1925).

**PROGNOSIS.**—The chances that a first or second attack of acute catarrhal appendicitis will be renewed are about 77 per cent.; but when a fourth or a fifth attack has occurred, the probability is very great that more will follow and ultimately end fatally, unless operation is performed.

After the patient has gone through an acute attack safely, and the characteristic tumor indicating an acute suppurative process is felt, a circumscribed peritonitis, rather than a general suppurative one, is likely to occur if another attack takes place.

**TREATMENT.**—Appendectomy is indicated at the first relapse, and when a tumor is present during the interval, the presence of septic accumulation, ulceration, or perforation being likely. It may be performed during a period of quiescence in the manner described in the preceding pages.

Out of 94 cases of operation for chronic appendicitis subsequently traced 66 were cured, 20 improved and 8 unimproved. Three of these 8 are believed to have had gastric ulcer at the time of the appendectomy. In other cases the failure is ascribed to hysteria and to visceroptosis. No patient should be regarded as having typical chronic appendicitis unless a history of a former characteristic acute attack is obtainable. More exploratory incisions should be used, in preference to the muscle-splitting incision, and always in atypical cases. C. J. Rowan (*Minn. Med.*, June, 1922).

Statistical and follow-up report on 500 cases of chronic appendicitis operated on at the University of Penna. Hospital from 1913 to 1920. There were 260 males and 240 females. The greatest frequency of the condition among males was in the first half of the third decade, and among females, during the period at which the menstrual function is established. The outstanding and almost constant symptom was periodic pain in the right iliac fossa. Evidence was found that a chronic process may progress without acute symptoms. There was 1 death (from intestinal obstruction by a congenital fold of peritoneum) in 355 patients operated on during a quiescent period, and 4 deaths among 145 cases operated on during an acute exacerbation. A normal appendix was removed in 3.8 per cent. of the 500 cases. Tuberculous appendicitis was found in 7 cases and carcinoma of the appendix in 1 case. Follow-up study showed complete relief of symptoms after operation in 83.1 per cent.; partial relief in 9.7 per cent., and no relief in 7.07 per cent. Deaver and Ravdin (*Arch. of Surg.*, Jan., 1923).

In persons without ptosis and not pronouncedly neurotic, tenderness in the right lower quadrant, especially when gastric symptoms are marked, usually justifies a diagnosis of appendicitis, and **operation** gives good results. Riesman (*Jour. Amer. Med. Assoc.*, Oct. 18, 1924).

When operative procedures cannot for one reason or another be applied, **dietetic and medical measures** should be resorted to, to limit as much as possible the morbid process. Red meats should not be allowed more than once daily, and a **farinaceous, vegetable, and milk diet** favored. Complete abstention from meats is sometimes necessary. Where any degree of gastric catarrh exists, **gastric lavage** with a **solution of sodium carbonate** (1 dram—4 Gm.—to the quart) every other day, with **bismuth** (10

grains—0.6 Gm.) twenty minutes before meals, are indicated. A **flannel bandage** so adjusted as to pass over the region of the appendix serves to protect the abdomen from sudden chilling, and is an excellent prophylactic measure.

Stress laid on ileocecal regurgitation and cecal mobility and stasis as causes of the symptoms of chronic appendicitis. In such cases the following measures are usually effective: **Elimination of meat** from the diet; a **yeast cake** night and morning; **abdominal massage, physical drill**, and a **corset** with an abdominal "lift," or even an ordinary **abdominal belt** with a rubber sponge under it. F. N. G. Starr (*Northwest Med.*, Sept., 1924).

The bowels should be kept free by the use of mild **saline aperients**, with **magnesia** as main active agent.

The chronically inflamed appendix appears to be only one evidence of a pathologic condition of the lower bowel featured by obstruction to proper evacuation, with resulting low-grade inflammation. Appendectomy alone is often inadequate treatment. The first step in the medical treatment is regulation of the bowels by means of an **increased fluid intake**, **increased ingestion of fruit**, and usually, **increased exercise**. The dose of **liquid petrolatum** should be that which can be taken without leakage. If not sufficient in itself, it will reduce the amount of other **laxative** (preferably liquid, for more easy adjustment of dosage) which may be necessary. If there is spasm of the bowel or incompetence of the ileocecal valve, **atropine** or **belladonna** will usually give relief. Most patients should be encouraged to increase and diversify their **diet**, as they eat too little. The roughage in the diet should be kept at a minimum. Fats, fried food and condiments should be restricted. Distress after meals may often be avoided by **lying down on the right side** for  $\frac{1}{2}$  to 1 hour after meals. **General ex-**

**ercise** (avoiding fatigue) is indicated to build up muscle tone, though at first **rest** is frequently more valuable. Support by a **brace** or **corset** should be avoided if possible. Over one-half the patients are greatly improved by such treatment, and are comfortable as long as they take care of themselves: Where appendectomy is necessary, any mechanical factors producing stasis should be corrected in addition. C. H. Lawrence (Boston Med. and Surg. Jour., Nov. 8, 1923).

**AFTER-TREATMENT OF THE VARIOUS FORMS.**—The patient should not leave his bed until the subsidence of all trace of inflammation and proper healing of the wound have taken place, namely: from ten days to two weeks. In cases with drainage a longer period may be necessary.

The *postsurgical treatment* is important and should be conducted with great care. The stomach should be given complete rest for twelve hours, **cracked ice** and **water** being allowed in moderation. After that, **liquid food**, beginning with **peptonized milk**, if there is any tendency to nausea or vomiting, may be given. To keep the intestinal tract as clear as possible, a daily **injection of lukewarm soap and water** is sufficient. A mild cathartic may be given after third day. The patient should lie on his back the first two days, then begin to change his positions in bed, if he desires, without violence. **Opium** should be given in small doses if pain is marked.

The outside dressing should be changed every day at first, and the packing removed on the fourth or fifth day after operation. In cases of limited abscess the drains should be started earlier. This should be done with great care and the cavity cleansed by dry sponging, no fluids being introduced into the wound. The wound is then repacked

and left so three days, and renewed when necessary. As the packing is renewed from time to time, it should be reduced in size at each sitting, to permit the wound to heal from the bottom.

The plan of **Murphy proctoclysis**, already described, should be followed whenever any but the slightest grade of peritonitis exists.

When symptoms persist after appendectomy, there is usually cecal enlargement, a pendulous tip and stasis, with or without adhesions. The cecum is more easily palpable than normally. Attacks are caused by the cecum failing to empty, due to diet, increased sag, muscle fatigue, and exhaustion from overwork. Daily **cecal massage**, directly after breakfast and supper, is helpful. It is a deep, flat-fingered, rotary movement, beginning with the sigmoid and following the colon to the cecum, the whole taking 15 to 20 minutes. It may be carried out either in dorsal recumbency, or in a modified knee-chest position where the cecum is very low. The patient also **lies down** after each meal **with a pillow under the shoulders** to hyperextend the chest and raise the abdominal organs. This is followed by a face position for  $\frac{1}{2}$  hour. In difficult cases the **hanging prone position** over the edge of the bed is used for 5 minutes often during the day. The **diet** should exclude scratchy residue and leave a large, soft bulk. Mild **catharsis** and periodic cleaning out may be indicated at first. **Deep breathing, rib stretching** and **abdominal muscle exercises** are prescribed. Often **rest in bed** for 4 to 6 weeks at first is necessary if the patient is to respond to the other measures. As the condition improves, exercise and massage are increased and laxatives reduced. The prognosis is excellent provided the patient will assist until the results are obtained. L. T. Swaim (Boston Med. and Surg. Jour., Nov. 8, 1923).

WILLIAM B. COLEY,  
New York.

**ARISTOL.**—This is an iodine compound used locally to enhance healing processes, prepared by adding a solution of iodized potassium iodide to an aqueous solution of sodium hydrate containing thymol. The dried precipitate, constituting a dithymol diiodide, occurs in the form of a reddish-brown, almost tasteless powder having an iodine-like odor and containing 45 per cent. of this element. It is readily soluble in collodion, ether, and chloroform, and slightly so in alcohol, but is insoluble in water and glycerin.

**PREPARATIONS.**—The compound is officially recognized as *Thymolis iodidum*, U. S. P. (thymol iodide).

It may be used as a *powder*; it adheres to the skin and if the latter is broken does not cause irritation. It does not have any appreciable toxic effects if absorbed. It is not very active as an antiseptic, and its germicidal action is limited, but it prevents infection and promotes very effectively absorption and cicatrization.

Aristol may be employed in the form of *ointment*, wax and lanolin being best fitted for this purpose. It is best used in strengths ranging between 5 and 20 per cent. It may also be employed, dissolved in lanolin, as an *oily spray* for the respiratory passages, a 5 per cent. solution being advantageous, with an oil atomizer.

**THERAPEUTICS.**—The value of aristol is especially noticeable in **ulcers** of various kinds, such as those due to **adenitis**, **chilblains**, **boils**, **varicose veins**, after careful disinfection with some antiseptic solution. This applies also to **burns** and **scalds** of the second or third degree. In any of these the powder or ointment can be used to advantage. In **vaccination ulcers**, I have seen it act with marked rapidity where other measures had failed. It favors the healing of superficial **wounds**; lacerations of the scalp, for instance, are made to heal with great rapidity. It is also efficient in **hyperidrosis** when used as a dusting powder. In **syphilitic ulcers**, **chancroids**, **buboes**, and venereal ulcerative processes in general, it has been found as effective as in simple ulcers. Aristol has given good results in indolent **corneal ulceration** when applied as a powder with a camel's hair pencil. The 5 per cent. ointment is useful in **blepharitis**. Powdered aristol blown over

the mucous surfaces is helpful in **ozena** and **chronic rhinitis**, as well as in ulcerations of the genital organs, **uterine erosions**, **endometritis**, and **eczema vulvæ**. S.

**ARNICA.**—This is the plant *Arnica Montana*, or leopard's bane, a perennial of the natural order Compositæ, indigenous to the mountains of northern Europe and Siberia, as well as to the western United States. The flowers are large and orange yellow, and there is a small, curved rhizome with several rootlets. The dried flower-heads are official. The plant contains an ammoniacal alkaloidal principle, *trimethylamine*  $[N(CH_3)_3]$ , which is doubtless the active ingredient. It contains also *arnicin*, inulin, capronic and caprylic acids, tannin, mucilage, resins, and two essential oils.

**PREPARATIONS.**—*Tinctura arnicæ*, N. F., a tincture of 20 per cent. strength, made from arnica flowers. Dose, 10 to 30 minims (0.6 to 2 c.c.).

A tincture of arnica root has also been prepared and used.

*Fluidextractum arnicæ*, N. F. Dose, 1½ minims (0.1 c.c.).

**PHYSIOLOGICAL ACTION.**—Locally applied, arnica acts as a *stimulant* and often a decided irritant, in case of a delicate skin, where it may produce not only burning and irritation, but even decided skin lesions.

**Internally**, arnica slows the heart, but seems to raise arterial pressure slightly and stimulate the vagus nerves; it also increases the action of the skin and kidneys. In large doses it is emetic and cathartic, causes great muscular weakness, a rapid pulse, and, if the dose be excessive, collapse. It appears to be eliminated by the skin and kidneys.

**THERAPEUTIC USES.**—Arnica has been used internally as an antipyretic and stimulant in typhus and typhoid fevers, as well as in concussion of the brain, delirium tremens, rheumatism, epistaxis, chronic dysentery, and paralysis of the bladder. The drug is seldom used internally nowadays, but externally is a popular remedy among the laity for **sprains** and **bruises**. When thus employed its irritating qualities should be borne in mind, especially in patients with tender skins. W.

**ARSACETIN.** See ATOXYL.

**ARSENIC** (Arsenum).—Metallic arsenic appears as a steel-gray, lustrous, brittle mass, which is odorless and tasteless. When heated to 140° C. or over, it emits an odor of garlic; the metal is volatilized, and becomes more or less rapidly oxidized, according to the temperature, to form arsenic trioxide,  $As_2O_3$ . The latter is the so-called “arsenic” used in medicine,—also known as white arsenic, arsenous oxide, arsenous anhydride, ratsbane, and, incorrectly, as arsenious acid.

Arsenic is prepared commercially from the native ore by a process of roasting and sublimation.

**PROPERTIES.**—When freshly sublimated, arsenic trioxide appears as an amorphous, vitreous, “glassy” mass. Upon absorption of moisture from the air, white, opaque crystals are formed, which constitute the “porcelain-like” variety of the oxide of arsenic. As generally dispensed, after being ground in a mortar, the product consists of a mixture of small amorphous particles and crystals, odorless, practically tasteless, and having the specific gravity 3.7. At ordinary temperatures arsenic trioxide dissolves but slowly in water, the glassy variety requiring 30 parts of the latter for solution, and the crystalline variety 100 parts. In boiling water, however, arsenic trioxide dissolves to the extent of 1 in 15 parts. Its solution is accompanied by the formation of arsenous or arsenious acid ( $H_3AsO_3$ ), of which arsenic trioxide is the anhydride. In alcohol, arsenic trioxide is but slightly soluble; in hydrochloric acid and solutions of alkalis or of carbonates of the alkali metals,

however, it is freely soluble. Glycerin dissolves it to the extent of 1 part in 5; the glassy variety alone dissolves in turpentine oil.

#### PREPARATIONS AND DOSE.—

The official preparations containing arsenic are as follows:—

*Arseni trioxidum* (arsenic trioxide; “arsenious acid;” white arsenic); dose,  $\frac{1}{60}$  to  $\frac{1}{12}$  grain (0.001 to 0.005 gram).

*Liquor acidi arsenosi*, containing 1 per cent. of arsenic trioxide; dose, 1 to 10 minims (0.06 to 0.6 c.c.).

*Liquor potassii arsenitis* (Fowler’s solution), made from 1 part of arsenic trioxide, 2 parts of potassium bicarbonate, and 3 parts of compound tincture of lavender, with enough water to make 100 parts; dose, 1 to 10 minims (0.06 to 0.6 c.c.).

*Liquor arseni et hydrargyri iodidi* (Donovan’s solution), containing 1 per cent. each of arsenous iodide and red mercuric iodide; dose, 1 to 5 minims (0.06 to 0.3 c.c.).

*Arseni iodidum* (arsenous iodide; arsenic tri-iodide), a reddish, crystalline powder, soluble with partial decomposition in about 12 parts of water, and in about 28 parts of alcohol; it is also soluble in chloroform, ether and carbon disulphide; dose,  $\frac{1}{12}$  grain (0.005 gram).

Mentioned in the National Formulary are or were the following preparations of arsenic:—

*Sodii arsenas* (sodium arsenate), occurring in colorless crystals, which are soluble in 1.2 parts of water and slightly soluble in alcohol; dose,  $\frac{1}{12}$  grain (0.005 gram).

*Sodii arsenas exsiccatus* (dried sodium arsenate), an amorphous white powder, soluble in 3 parts of water and very sparingly soluble in alcohol;

it is nearly twice as strong as the preceding preparation; dose,  $\frac{1}{20}$  grain (0.003 gram).

Liquor sodii arsenatis, containing 1 per cent. of exsiccated sodium arsenate; dose, 1 to 10 minims (0.06 to 0.6 c.c.).

Liquor sodii arsenatis dilutus (Pearson's solution), containing about 0.1 per cent. of crystalline sodium arsenate and being therefore 10 times weaker than the solution of sodium arsenate; dose, 30 minims (2 c.c.).

Liquor auri bromidi et arseni (solution of gold bromide and arsenic). Each 3 minims (0.2 c.c.) contain  $\frac{1}{90}$  grain (0.0007 gram) of bromauric acid and the equivalent of  $\frac{1}{125}$  grain (0.0005 gram) of arsenic trioxide; dose, 3 minims (0.2 c.c.).

Liquor potassii arsenatis et bromidi N. F. III (Clemens's solution), made by boiling arsenic trioxide and potassium carbonate together in water, adding pure bromine, and shaking the mixture repeatedly until it remains clear. Contains 1 per cent. of arsenic trioxide and 2 per cent. of bromine; dose, 1 to 5 minims (0.06 to 0.3 c.c.).

Arsenic is also contained in the following organic compounds: Cacodylic acid (*q.v.*) and cacodylates, atoxyl (*q.v.*), soamin (*v.* Atoxyl), arsacetin (*v.* Atoxyl), arsenophenylglycine (*v.* Atoxyl), arrhenal (*v.* Cacodylic acid), and dioxydiamidoarsenobenzol (*q.v.*) and its allies.

**MODES OF ADMINISTRATION.**—Where arsenic is to be given internally in liquid form, Fowler's solution (liquor potassii arsenitis) or the liquor sodii arsenatis may be used; either preparation should be given after meals, freely diluted in water, as the drug is irritating to

mucous membranes. For administration in pill form, the trioxide is well adapted. The drug is generally given either in ascending doses, beginning with small amounts and then gradually increasing; or, less frequently, in descending doses, beginning with the maximal amount and gradually decreasing. The first of these methods is the safer, since in some patients intolerance even to moderate doses of arsenic is encountered. For administration of full doses in cases where the gastrointestinal tract is irritable or has rebelled, the subcutaneous method is available. A good preparation of Fowler's solution, containing no free arsenous acid, diluted with distilled water, may be employed for this purpose, provided strict aseptic precautions be taken; the preference is now given, however, to the less irritating organic combinations of arsenic, especially the cacodylates, *q.v.*

Moyer, in 28 cases of chorea, used a solution of pure anhydrous sodium arsenate, obtaining satisfactory results.

The rectal mode of administration of arsenic has been tried out and recommended by Renaut, who gave injections of  $\frac{1}{20}$  grain (0.003 Gm.) of the trioxide in  $1\frac{1}{4}$  drams (5 c.c.) of water three times daily in early cases of tuberculosis and in diabetes mellitus and exophthalmic goiter. He found that this treatment could be continued for months without causing gastric disturbance. Where rectal irritation appeared, a few drops of laudanum were added to the solution given.

Arsenic is well borne by children, and may be given to them, if necessary, in doses relatively larger than



are generally tolerated by adults. At all ages, however, it is desirable, owing to the fact that arsenic tends to accumulate in certain of the viscera, to suspend its administration for a week or ten days after it has been given steadily for a period of two to eight weeks (according to the doses given).

**INCOMPATIBILITIES.**—Liquid arsenical preparations are incompatible with most of the metallic salts, including especially those of silver, iron, copper, calcium, and magnesium. In prescribing the arsenical liquors, care should be taken to avoid chemical incompatibility by observing the reaction of the preparations with which they are to be combined: In acid solutions the liquor acidi arsenosi should be used, in alkaline solutions the liquor potassii arsenitis, and in neutral solutions the liquor sodii arsenatis.

**CONTRAINDICATIONS.**—Arsenic is contraindicated in acute skin diseases with local discomfort and evidences of an active inflammatory process. In inflammatory affections of the gastrointestinal tract its use is also, in general, unwise, though in cases presenting vomiting as the only or most prominent symptom its administration is permissible and even, it is claimed, sometimes beneficial. In acute infections with fever,—an exception being sometimes made in the case of malaria,—arsenic is also considered harmful.

Symptoms of beginning intolerance such as anorexia, digestive disturbance, conjunctival irritation, and swelling of the eyelids, should be watched for in patients taking arsenic, and their appearance be taken as a signal to interrupt for a time the use

of the remedy, or, at least, to stop the progressive increase in the dosage.

**PHYSIOLOGICAL ACTION.**—

**Local Effects.**—Arsenic preparations act as slow caustics. Brief contact of arsenicals with the skin does not affect the latter, but their more prolonged presence, even in relatively high dilution, results in local hyperemia and the production of a vesicular or pustular eruption. It differs from most other caustics in affecting especially the living cells, dead tissues remaining uninfluenced. The pain produced as a result of its caustic effect is slight in comparison with that of strong acids and alkalies. Correspondingly, the subcutaneous injection of arsenic compounds, uncombined with other irritants, does not give rise to any great degree of pain. Mucous membranes, however, seem to be more sensitive to its irritating action, considerable discomfort, as well as destruction of tissue, being produced.

**General Effects.**—*Nervous System.*—Small doses of arsenic repeatedly given may be said to stimulate the nervous system as a whole. Some direct effect of the drug on the nervous tissue is believed to be exerted, though, as is the case with most other drugs, no definite information is as yet available concerning the exact chemical or physicochemical changes it induces. A continuance of the stimulating effect, as in chronic arsenic poisoning, results in inflammation of the peripheral nerve tissues, *i.e.*, neuritis, which involves the possibility of ultimate degeneration and loss of function.

Where the drug is taken in larger amounts, the stimulation produced is more sudden and less likely to lead to inflammation. The secondary effect is

then a depression or paralysis of function more immediate than that succeeding inflammation, and which may, through involvement of the medulla, with its centers of respiration and vasomotor action, produce death by respiratory failure—the common termination in fatal acute arsenic poisoning. It should be borne in mind that even a single dose of arsenic, poisonous but not large enough to cause prompt death, may produce neuritis.

Examining the effects of acutely toxic doses of arsenic on the nervous system more closely, we find that the sensory apparatus is generally the earliest affected. The frog poisoned with arsenic exhibits a descending paralysis the successive manifestations of which are loss of spontaneous movements, insensibility to mechanical and chemical stimuli,—showing paralysis of sensation,—and finally motor paralysis. That ligation of the artery to a limb before injection of arsenic—thus preventing the drug from reaching the extremity after its absorption—does not prevent the loss of sensation and motile power in that limb, shows that the paralyzing effect is produced on the centers rather than at the periphery.

*Circulation.*—The chief circulatory effect of arsenic is a lowering of the tonicity in, or actual paralysis of, the walls of the capillary vessels, especially those of the gastrointestinal tract. The improved state of nutrition brought about by “tonic” doses of arsenic may in part be the result of a relative hyperemia and consequent greater functional activity of the alimentary organs. In any doses but the smallest, however, the hyperemia verges upon or actually amounts to an inflammation; the permeability of the dilated capillaries is so increased that a large amount of fluid

escapes from them, lifting up the superficial mucous layers of the gut from the subjacent tissues, and the result is a profuse, watery diarrhea containing varying amounts of shreds of the mucous membrane and extravasated red blood-cells. This action on the capillary vessels is believed to be exerted directly on them,—not through the intermediary of any centers of vasomotor regulation. If a large dose of arsenic be injected intravenously into a mammal the vascular dilatation produced is so extensive that a marked fall in the blood-pressure occurs. Pronounced hyperemia of the gastrointestinal tract is also seen, indicating that the low pressure is due, at least in major part, to recession of blood into the splanchnic vascular area.

Though not as yet experimentally proven, it appears reasonably certain that the edema witnessed in chronic arsenic poisoning is due to dilatation and increased permeability of the capillaries of the parts concerned. This is in agreement with the fact, mentioned by Sollmann, that intravenous injection of large amounts of salt solution will produce edema in animals subjected to arsenic, whereas in the normal animal it will not.

Upon the heart arsenic clearly does not possess the marked depressant effect of the closely allied metal, antimony. Massive doses of the former, however, do seem to weaken the heart sufficiently to prove a contributory factor in the fall of blood-pressure produced by intravenous injections of arsenic preparations. Whether the vasomotor center is appreciably depressed by toxic doses of arsenic is not definitely known.

*Respiration.*—No significant effects upon the breathing are exerted by small

doses of arsenic taken by the mouth. Injected intravenously, arsenic preparations tend at first to increase the respiratory rate. Lethal doses arrest the respiration before cardiac arrest occurs; this does not necessarily indicate, however, a direct effect of the drug upon the centers in the medulla, which may be influenced indirectly through the circulatory changes.

*Alimentary Tract.*—Whether taken by mouth or injected under the skin, arsenic exerts its earliest effects upon the intestinal tract, causing, as has already been said, a dilatation of the capillary vessels corresponding in its extent with the dose taken. Subcutaneous injection of the drug induces this effect just as readily as oral ingestion; hence it is evident that the action of arsenic is not, as formerly thought, that of a locally acting, corrosive agent,—especially in view of the fact that the proportion of arsenic excreted from the general system into the alimentary tract is very small (Sollmann). The gastroenteritis produced by excessive amounts of arsenic differs from that of true corrosives in being accompanied by a profuse, serous diarrhea, owing to the greatly increased permeability of the dilated and paralyzed capillaries.

While vascular changes will account for most of the effects in the gastrointestinal tract, they fail to explain the cloudy swelling and fatty degeneration of the epithelium which may also be witnessed. The presence of an additional direct effect of arsenic on the cells, comparable to that of phosphorus, would thus seem to be indicated. This cellular effect is not limited to the alimentary tract, but involves other glandular and muscular organs.

Small doses of arsenic improve the appetite and are credited with the power to enhance the digestive processes. Whether these effects are due to a mild vasodilator action or to a direct action on the cells is not known.

*Skin.*—Prolonged use of large doses of arsenic exerts a pronounced influence upon the skin. The growth of the epithelium is stimulated, causing the superficial layers to become thicker than normal. According to Jamieson, arsenic gives rise to hyperidrosis of the palms and soles by stimulating the sweat-glands, then to the formation of warty corns, and finally to a diffuse hyperkeratosis, associated with burning sensations. General pigmentation is also in some cases caused by arsenic, owing to the deposition of some dark-colored material—not an arsenic compound—in the dermis. Skin eruptions frequently occur in arsenic poisoning. In extreme cases, degeneration of the skin may ensue.

If arsenic is fed to horses and sheep there is improvement in the condition of the hide, as well as an increase in size. Feeding arsenic to rabbits will make them grow to enormous size (Gies).

Epithelium shows an extraordinary affinity for arsenic. There is a variety of skin lesions in arsenic poisoning.

The drug is carried to the basal layer and passed on from cell to cell, being finally cast off in the desquamating scales and hairs. The changes produced are essentially nutritive, the tissues in the early stages presenting a condition of well-being. Under continued action, degeneration processes and deposit of pigment take place. Still later there is atrophy, and the epidermis may be very much reduced in thickness. In very advanced cases there is degeneration of the glands of the skin. Washburn (Wis. Med. Jour., Oct., 1911).

*Blood.*—It would seem established by clinical experience that in certain forms of anemia, such as progressive pernicious and posthemorrhagic anemias, arsenic tends to stimulate the formation of red blood-corpuscles. Under normal conditions, however, its effects, as observed in experimental work, are not such as would confirm this effect of arsenic. Thus Stockman and Charteris, investigating the changes produced by arsenic in the bone-marrow, observed merely an increase in the number of leukoblastic or leukocyte-producing cells, together with increased vascularity and atrophy of fat-cells. Stockman and Greig did not find any increase in the number of red cells or hemoglobin percentage upon administering arsenic to normal animals. Bettman found in rabbits that slowly toxic amounts of arsenic caused the appearance of nucleated red blood-corpuscles in the blood, though the total number of erythrocytes and also the hemoglobin percentage were reduced. More recently the effects of arsenic in anemia have been ascribed to an anti-hemolytic action. It was demonstrated *in vitro* that in the presence of arsenic the resistance of the erythrocytes to dissolution by hypotonic solutions is increased. Since in many cases of anemia a hemolytic factor tending to destroy the red cells is believed to be at work, such a preventive influence on the part of arsenic would obviously be advantageous, and Hill has suggested this as an explanation of the improvement witnessed under arsenic in anemias. This, to be sure, would constitute mere palliative treatment, since the actual cause of the hemolysis is not held to be overcome by the drug.

According to Duncker and Iodlbauer, small doses of arsenic increase the catalytic action of the blood.

In a series of experiments in which he mixed arsenic in a suspension of blood-corpuscles, the writer showed that arsenous acid is fixed to the red blood-corpuscles, that this process takes place very rapidly, and, furthermore that it protects these corpuscles against the hemolytic action of distilled water. He believes that the arsenic affects the stroma of the red cells in the hemoglobin, but this stroma is known also to contain lecithin and cholesterin. J. A. Gunn (Brit. Med. Jour., July 18, 1908).

Arsenic, whether in the form of sodium arsenite or sodium arsenate, exerts on the red blood-corpuscles an action antagonistic to that of certain hemolytic agents. In a previous paper the writers pointed out that very dilute solutions of arsenous acid exert on the red blood-corpuscles *in vitro* a distinct protective action against hemolysis by hypotonic saline solutions. In the later experiments, however, hemolytic agents of diverse nature were employed, namely, distilled water, cyclamin, and sodium glycocholate. These experiments account for the as yet imperfectly explained benefit which results from the medicinal administration of arsenic in pernicious anemia. Gunn and Feltham (Brit. Med. Jour., Jan. 21, 1911).

In the examination of 123 cerebrospinal fluids collected at intervals ranging from 5 minutes to 23 hours after intravenous injection of from 0.3 to 0.6 Gm. (5 to 10 grains) of arsphenamin, 38 revealed appreciable amounts of arsenic. The largest found was 0.6 mg. of arsenous oxide in 10 c.c. The average amount was 0.18 mg. The shortest interval at which arsenic was found was 30 minutes; the longest 2 hours. With successive injections, the fluids in general show progressively smaller amounts of arsenic for the same interval. Rieger and Solomon (Jour. Amer. Med. Assoc., July 6, 1918).

Minimal doses of arsenic inhibit oxidation and stimulate growth and metabolism as well as hematopoiesis. As the hematopoietic effect does not occur in thyroidectomized persons, the action is dependent upon stimulation of the thyroid hormone. F. Muller (Deut. med. Woch., June 23, 1922).

In a study of the action of arsenic on the leukocytes, there was observed a decrease of the neutrophils; the absolute number of the lymphocytes, however, remained unchanged, a relative lymphocytosis thereby resulting. Haase (Munch. med. Woch., May 22, 1925).

*Nutrition and Metabolism*—Small doses of arsenic are frequently credited with the power to improve general nutrition. In young animals, growth appears to be stimulated by it. Though Stockman and Greig observed experimentally that only the development of the bones was favored, Gies, working with young rabbits, found that animals given very small amounts of arsenic showed greater body weight, with better muscular and adipose development, than their untreated fellows. Nitrogenous excretion, and also carbon-dioxide excretion, are somewhat diminished by small doses of arsenic, according to certain observers. Weiske claims that with arsenic a greater proportion of the food is taken up by the alimentary tract than normally, and that less protein destruction occurs in the tissues, thus accounting for the favorable nutritive state resulting. It seems quite plausible that the first of these effects should result from a state of slight capillary dilatation in the gastrointestinal tract such as would probably be produced by moderate doses of arsenic, the various digestive functions, including absorption, being therefore better

performed. The diminution of protein destruction in the tissues, however, is not by any means established.

The writer calls arsenic the digitalis of metabolism. In an experimental research on its action, he found that animals fed with arsenic developed much better in every respect than the controls from the same litter. That this better physical development includes the vital tissues and is not merely increased accumulation of fat is shown by the fact that the total tissues of the animals ground into a homogeneous mass, from which water and fat were extracted, showed a larger proportion of nitrogen in the arsenic animals than in the controls. He fed dogs with arsenic; one of the dogs, a fox-terrier, he thinks, must be accorded the record for eating arsenic, as he took 0.5 Gm. of arsenic daily for two months and then 2.6 Gm. a day without harm, the arsenic feeding being kept up for over two years. Cloetta's further research, however, swept away the idea that the animal had become habituated to the drug, as it was proved that he merely had ceased to absorb it. The lining of the alimentary canal had evidently become modified in such a way that it ceased to absorb the arsenic. Cloetta (Corresp.-Blatt f. schweizer Aerzte, July 20, 1911).

In a study of the effects of arsenic on the development of the bones in rabbits, the writer found that small doses had little influence on the general state of nutrition, bodily development or length. Bones were, however, rendered denser, heavier and more resistant. A. Van den Eckhout (C. r. Soc. de Biol., Oct. 22, 1921).

Study of the phosphates, acidity and ammonia in the urine in patients receiving arsenic showed these factors to be increased in the majority of cases. This supports earlier observations on respiratory metabolism pointing to reduced oxidation as a factor in the anabolic effect of arsenic. Kramár and Tomcsik (Klin. Woch., Jan. 15, 1924).

In poisoning by arsenic, distinct metabolic changes are to be observed. Nitrogenous metabolism is unmistakably increased, the amount of nitrogen passed in the urine being clearly augmented. A more or less characteristic effect is the rapid and complete disappearance of the glycogen from the liver. Sarcosine is simultaneously formed and the alkalinity of the blood diminished. Glycosuria is no longer produced by Claude Bernard's puncture of the medulla in arsenic poisoning. Fatty degeneration of the epithelia, not only of the gastrointestinal tract, but also of the kidneys and liver, as well as of voluntary muscle tissue and that of the heart and vessels, also results. The phenomena resemble closely in most respects those of phosphorous poisoning, though not quite so pronounced. Jaundice may be an accompaniment of arsenic poisoning, owing to the changes produced in the liver.

Experimental findings that the kidneys of animals given lethal doses of arsenous acid, salvarsan, neosalvarsan, galyl, arsenophenylglycin, atoxyl, and arsacetin are separable into two extreme groups, the red and the pale kidneys, with transitional types in which the predominating changes ally them more closely with the one group or the other. In the group of red kidney, congestion and hemorrhage are the dominant features of the arsenic action, while in the pale kidneys, the dominant lesion is tubular. Pearce and Brown (*Jour. Amer. Med. Assoc.*, Sept. 25, 1915).

That arsenic in toxic amounts causes cell death by interference with the oxidative processes governed by glutathione is the conclusion resulting from the writers' researches. Hopkins had already found that compounds containing the SH group were concerned in processes of oxidation and reduction and isolated such a

compound, known as glutathione, from tissues. Voegtlin and his co-workers found an SH compound in trypanosomes, to which arsenic is toxic, and believe that this agent in certain trivalent forms is a specific poison for the SH group. C. Voegtlin, H. A. Dyer and C. S. Leonard (*Pub. Health Rep.*, Aug. 17, 1923).

**ABSORPTION AND ELIMINATION.**—Arsenic in inorganic combination is rapidly absorbed into the system, whatever be the mode of introduction. Even when it is applied to the intact skin, sufficient absorption may take place to induce poisoning. Organic preparations in which the element arsenic is not present in the form of an oxide, but is directly bound to carbon, as in arylarsonates, do not, however, exert their effects so promptly, as the arsenic has first to be oxidized through the agencies residing in the body tissues, possibly into the form of an arsenite—before the familiar “arsenical” effects can be produced.

Scherbatscheff found through experiments on dogs that, even after therapeutic doses, arsenic remains for a long time in the organism, more especially in the brain and bones. After subcutaneous injection, the longest period noted by him was 160 days. After a short period of administration, it was found longest in the brain; but after more extended periods it was retained longest in the bones.

The elimination of arsenic is very gradual. Injected into the bloodstream, it is found rapidly to disappear from the latter and to become deposited in the tissues, in which it is held to enter into a firm combination with the nucleins. Repeated administration of the drug leads to its storage, not only in parenchymatous

organs such as the liver, spleen, kidneys, and lungs, but also in the walls of the gastrointestinal tract and, to a certain extent, in the muscles, bones, and nervous system. The excretion of arsenic takes place with the urine, feces, sweat, the epithelium shed from the skin, and, in nursing women, usually to a certain extent in the milk. Though its elimination begins within a few hours after exhibition, the major portion of a single dose of arsenic is not removed from the body for a number of days. According to Cushman, but one-fifth of the total amount of arsenic is lost with the urine and stools. A considerable proportion has been found to be very gradually eliminated in the superficial layers of the skin and in the hair, in which it may be detected for months after cessation of its use. In the urine of experimental animals it has been detected for as long a period as 160 days after its administration had been stopped. It is excreted in the urine partly in organic combination.

Arsenic was found by Armand Gautier to be a normal constituent, in small amounts, of the human thyroid gland, and was also detected by him in the thymus, the brain, the skin, and in some instances in the hair, as well as in the mammary glands of a cow and in her milk. He did not find it, however, in various other tissues which he examined. Though Hödlmoser subsequently denied the presence of arsenic in any tissue of the normal body, Bertrand in 1903, in a series of experiments on animals, was able to confirm the findings of Gautier and even went farther, concluding that arsenic is a normal element of the living cell and is to be found in all animals and all organs.

The writers studied the ability of uterine glands to store arsenic as a cause of menstruation. Armand Gautier had maintained that the thyroïdal arsenic was discharged in the menstrual blood. The authors found that the arsenic discharged in the menstrual blood does not come from the thyroid, but from uterine glands, which act specifically as repositories for arsenic. M. Ries and J. Ries (*Münch. med. Woch.*, May 14, 1912).

The view that arsenic is retained during pregnancy was confirmed by the writer in rabbits, human fetuses and the organs from pregnant cadavers. The organs of a young man who had succumbed to Banti's disease showed quite a large proportion of arsenic. It was positively known that he had taken no arsenic during eight months at least before his death. In all organs examined arsenic was found in amounts ranging from traces to considerable proportions. Frommer (*Arch. f. Gynäk.*, ciii, No. 2, 1914).

From a large series of tests in persons taken at random, the conclusion was reached that arsenic is undoubtedly a normal constituent of the body, depending on dietary conditions and medication. Arsenic may be regarded as a normal constituent of hair, although occasional persons may be found whose hair does not contain it. Milk from normal persons should contain practically no arsenic; its presence should be considered as indicating therapeutic medication or ingestion in certain types of food. Arsenic is found in almost all babies. Arsenic is not as uniformly present in the blood as in the urine; it should not exceed 0.3 mgm. per 100 Gm. of dried blood specimen. Any excess over this is an indication of ingestion by food or medication. Exceedingly large amounts lead to the inference that the patient has been receiving medication, provided the history or serum test shows that syphilis is present. C. N. Myers and L. H. Cornwall (*Amer. Jour. of Syph.*, Oct., 1925).

**ACUTE ARSENIC POISONING.**

—This may arise in many ways, arsenic being a constituent of many chemicals used in manufacturing and for household purposes. Paris green (copper acetoarsenite) and Scheele's green (copper arsenite), contained in rat poison and other parasitocides, have given rise to a number of cases of poisoning in human beings. Fly paper and fly powders contain arsenic in considerable quantities. Acute poisoning has been known to occur by inhalation of the fumes of candles colored with Scheele's green, from ingestion of candy containing arsenic, from application of arsenical plasters to skin cancers, from inhalation of arsine gas in chemical laboratories, from the use of cosmetics, etc. Haberda reported the case of a servant-girl who committed suicide by introducing white arsenic into the vagina.

The symptoms of acute arsenic poisoning, with the exception of a sweetish, metallic taste and a sensation of heat in the mouth, which may appear very promptly, come on usually in one-half to three-fourths hour after the ingestion of the drug, and consist at first of dysphagia, burning pain in the esophagus and stomach, and nausea. Later the pain increases, vomiting occurs, and a profuse, watery diarrhea sets in. Blood may appear in both vomitus and stools, but more characteristic of the latter is the appearance in them, after diarrhea has persisted for a short time, of small shreds of the intestinal mucous membrane which, together with the serous fluid issuing from the paralyzed and very permeable capillary vessels of the gastrointestinal walls, finally constitute almost the whole bulk of the dejecta, and bring them into the same category as the "rice-water" stools of cholera

Asiatica. The marked loss of fluid from the body induces an excessive thirst; the skin becomes pale and cold; the urine is scanty or suppressed, frequently albuminous in so far as it is secreted, and headache, giddiness, together with cramps in the limbs, may appear. A state of collapse, with the rapid, feeble pulse and dyspnea, is then seen, which may be ascribed either to insufficiency of blood-supply to or direct depression of the medullary centers, together with enfeeblement of the heart muscle owing to a toxic effect of the drug upon it. Coma and occasionally convulsions precede death.

In certain cases variations from the above description may occur. Symptoms of collapse may appear promptly and suddenly, and the poisoning run its course with but little pain and gastrointestinal disturbance. A few cases are associated with pronounced evidences of nervous excitation, such as restlessness and delirium, while others, on the other hand, simulate the effects of a narcotic, sleep and coma being the prominent features.

The minimum fatal dose of arsenic is generally stated as  $1\frac{1}{2}$  or 2 grains (0.09 to 0.13 Gm.). Reese considers, however, that such an assertion rests on insufficient evidence, and believes that 10 grains (0.65 Gm.) comprise the amount that will prove fatal in most untreated cases.

Much larger amounts than those mentioned above have been recovered from, a large part of the drug ingested having probably failed to enter the system owing to vomiting induced by it. It is well to bear in mind, however, that idiosyncrasy may cause even minute doses to prove toxic, and that it is advisable always to begin with small doses.



Katchkatchev has reported an instance of remarkable idiosyncrasy toward arsenic in a student suffering from malaria who had begun to take Fowler's solution, beginning with 2 drops (0.12 c.c.) at a dose. Three hours after the first dose he presented all the classical symptoms of acute arsenic poisoning; nausea, vomiting, diarrhea, tenesmus, enteralgia, spasmodic cough, and paresis of the extremities. All these disturbances passed away by the following morning. Not suspecting the cause, the patient took another dose of 3 drops (0.18 c.c.) and soon the symptoms recurred so violently as to require antidotes.

Seven cases found in literature in which large amounts of arsenic, up to 60 Gm. (2 ounces), failed to cause death. In every case, except in 1 arsenic-eater, the patient vomited. It is therefore difficult to determine from them exactly the effective dose. In a personal case, the patient took 12 Gm. (3 drams) of arsenic with 1.4 Gm. (22 grains) of morphine. Neither vomiting nor diarrhea occurred, probably on account of the morphine, and the stomach was pumped out after 24 hours. Polyneuritis developed, lasting 9 months. The patient's hair gave a distinct arsenical reaction 3 months after the poisoning, but none after 9 months. G. Joachimoglu (Berl. klin. Woch., Jan. 21, 1922).

Twenty-eight cases of arsenic poisoning from the drinking of cider kept in a barrel which had contained an arsenic compound for spraying trees. Thirteen patients died, 10 in the acute stage and 3 in the subacute stage into which they had passed with cessation of the acute symptoms on the second day. The first death occurred in 6 hours; the tenth, in 45; the eleventh, on the 5th day; the twelfth, on the 22d day, and the last, on the 30th day. Lawson, Jackson and Cattanach (Jour. Amer. Med. Assoc., July 4, 1925).

The usual period of survival in fatal cases ranges from about ten to forty-eight hours. Taylor, cited by Reese, reported the case of a youth who succumbed in twenty minutes, after

showing symptoms of a tetanic character. This is, however, the shortest period on record. Frequently the patient lives over twenty-four hours after ingesting the fatal dose. In some cases, in which the amount absorbed has not been sufficient to cause early death, life is prolonged for from two days to a week, or even longer. In these patients, a diminution in the vomiting, purging, and pain may take place at the end of twenty-four or forty-eight hours; circulatory embarrassment, thirst, and albuminuria continue, however, and in a short time edema, cyanosis, cramps, and convulsive phenomena make their appearance, followed by coma and death. A skin eruption sometimes appears in these delayed forms of arsenic poisoning.

Report of 2 typical cases of industrial poisoning with arseniuretted hydrogen. One patient had had two similar but milder attacks one and three years before. In both cases there was an olive-green tint of the skin, probably the result of the combination of anemia and jaundice. Both patients were taken suddenly with headache, chilliness, vomiting, fever, hemoglobinuria, appearance of large amounts of bile in the stool, slight enlargement and tenderness of the liver, and enlargement of the spleen. The symptoms came on after working for a few hours plating lamps with a mixture containing hydrochloric acid, zinc, and arsenic. The patients lay in a state of stupor for a week; then one rapidly recovered. The other displayed more of a hemorrhagic diathesis, and intercurrent typhoid the third week brought him to death's door, but he finally recovered, although convalescence was delayed by a hemorrhagic nephritis. A special feature of the blood picture was the large numbers of erythroblasts, up to 3544 per c.mm. in the first and 43,377 in the second

case. Joachim (Deut. Archiv f. klin. Med., c, Nu. 1 and 2, 1910).

In cases which do not end fatally, disturbances of digestion, sensation, and motion are apt to delay the final recovery. The sensory phenomena witnessed include anesthesia, hyperesthesia, pain, etc. Motor paralysis may lead to early atrophy of muscles, but in these cases there is a marked tendency to subsequent recovery of function. Of 100 cases of arsenical paralysis studied by Imbert-Gourbeyre all but 3 recovered according to Horatio C. Wood, Sr.

Arsenical paralysis giving the same symptoms in 3 members of the same family. Arsenic was contained in some flour which all the patients had eaten. All 3 were seized with symptoms of acute arsenic poisoning, and within a fortnight developed the same symptoms of arsenical paralysis. They were troubled with anesthesia and paresthesias in the extremities, inability to work and to walk. The gait was unsteady and they were unable to stand with feet close together. Their walk was slow, rigid, and irregular. There was left facial paresis and abolition of the tendon reflexes, but no affection of the sensory nerves and no paresis of the upper extremities, save that in 1 of the 3 patients there was slight paresis of the fingers and thumb. The peculiar feature of these cases was that the paralysis was identical in all 3 instances, possibly owing to hereditary peculiarities. Luigi Ferrannini (Riforma medica, June 3, 1903).

Case of a man of 39 who had presented for 3 months symptoms of pseudotabes from arsenical peripheral polyneuritis. The condition is ascribed by the writer to poisoning from arsenic with which the drinking water in the Bell Ville region, Argentina, is known to be impregnated. Zayas (Semana Medica, Buenos Aires, Jan. 10, 1918).

**DIAGNOSIS OF ACUTE ARSENIC POISONING.**—The most characteristic and prominent symptom being a watery diarrhea, the chief conditions to be excluded are cholera nostras and cholera Asiatica. In the absence of a history of taking the poison, diagnosis may be extremely difficult. The Asiatic form of cholera, however, may be practically ruled out where no epidemic of the disease is known to be present. In cholera morbus the diarrhea is less likely to be associated with the passage of shreds of mucous membrane and blood than in arsenic poisoning, and the pain in this form is also generally less marked. Chemical tests upon the excreta may, nevertheless, in a few cases be the only means of differentiation.

From poisoning by strong acids or alkalies, arsenic poisoning is distinguished by the absence of corrosion of the mouth and throat, while from poisoning by metals such as mercury and lead the greater rapidity of onset will afford differential evidence.

Of the *pathological changes found post mortem*, evidences of gastroenteritis are the most prominent. The gastric mucosa is markedly reddened, either diffusely or in patches. It is often abnormally soft and may be covered with a sticky magma consisting of exuded mucus mixed with arsenic. Ulceration, however, is rarely present. Various parts of the intestine may show lesions corresponding to those present in the stomach; most frequently the upper portion of the small intestine, the cecum, and the rectum are involved. The gut may be found filled with watery fluid containing loose shreds

of mucous membrane. Upon microscopic examination the epithelial cells of the intestinal mucosa show pronounced granular or fatty changes. It must be noted, however, that in occasional instances all evidences of irritation of the gastrointestinal tract are unaccountably wanting (Reese).

Other organs, such as the liver, kidneys, and even the muscles, may show alterations of their parenchyma analogous to those found in the alimentary tract. More frequently, however, hyperemia is alone present. Changes in the central nervous system may in some instances be detected. Thus Erlicki and Rybalkin, according to Wood, found myelitis in a case of arsenic poisoning. Popoff, experimenting upon dogs, likewise noted myelitis, and, in cases where the period preceding death was longer than usual, observed granular changes in the protoplasm, shrinkage of the nuclei, and vacuolization, in the cells of the spinal gray matter. Alexander, on the other hand, found atrophy of peripheral nerves and changes in the muscle tissue of rabbits poisoned with arsenic (Wood).

The authors tested the action of arsenical compounds on the adrenals on male guinea-pigs and also on rabbits and dogs by intravenous administration.

The compounds tested comprised arsenous and arsenic acids, sodium cacodylate, atoxyl, arsacetin, arsenophenylglycin, salvarsan, and neosalvarsan. Sterile solutions of the substances were injected intraperitoneally in black and in white animals respectively. The writers conclude as follows: (1) Toxic doses of all arsenicals produce definite pathological changes in the adrenals of guinea-pigs. These include congestion, hemorrhage, disturbances in the lipid content, cellular degenerations

and necroses, and reduction in the chromaffin content. (2) The character and severity of the injury produced by different arsenicals varies with the chemical constitution of the compounds. (3) From these facts they believe that adrenal injury is an important factor in arsenical intoxication. Brown and Pearce (Jour. of Exper. Med., Nov. 1, 1915).

As a rule, the cadavers of victims of arsenic poisoning remain well preserved for a long period after death, owing to the inhibitory effect of the drug on putrefactive bacteria. In a few instances, however, decomposition has been known to progress as usual notwithstanding the presence of arsenic.

**TREATMENT OF ACUTE ARSENIC POISONING.**—The first consideration is to secure a quite thorough evacuation of the stomach by washing it out repeatedly with the aid of a stomach tube or giving an emetic. There is official in the U. S. Pharmacopeia a chemical antidote for arsenic,—*ferri hydroxidum cum magnesiæ oxido*,—which is made as follows: Mix 10 drams (40 c.c.) of liquor ferri tersulphatis with 4 ounces (125 c.c.) of water. Rub  $2\frac{1}{2}$  drams (10 grams) of magnesium oxide with cold water to a smooth, thin mixture, transfer to a one-liter bottle, fill the latter three-fourths full with water, and shake. Add the magnesia mixture gradually to the ferric sulphate solution in another bottle and shake. There is thus formed a precipitate of ferric hydroxide, which is believed to enter into a loose chemical combination with the arsenic, thus fixing it and tending to impede its toxic action. It is necessary that the preparation be fresh, and that it be given in large amounts, *e.g.*, in rapidly repeated

tablespoonful doses until 4 ounces (125 c.c.) have been administered, after which its evacuation from the stomach with the combined arsenic should be secured, and a **saline or castor-oil purge** then given. Where the official antidote or its ingredients are not quickly obtainable, other solutions of iron salts, such as the **tincture of ferric chloride**, **Monsel's solution**, etc., together with **magnesium carbonate**, **sodium carbonate**, or any alkali, may be used. The precipitate of iron hydrate should preferably, under these circumstances, be placed on muslin and washed with water. **Dialyzed iron**, freshly precipitated with a small amount of alkali, or freshly **calcined or precipitated magnesia** alone, can be used as inferior substitutes for the official antidote in an emergency. It should be stated that the implicit confidence hitherto placed in **ferric hydroxide** as an antidote has of late been somewhat shaken through experiments performed by De Busscher and essentially confirmed in 1923 by McGuigan *et al.* in an investigation undertaken at the request of the U. S. Pharmacopœial Revision Committee. The use of **sodium thiosulphate** intravenously in doses of  $7\frac{1}{2}$  grains (0.5 Gm.) or by mouth in doses of 30 grains (2 Gm.) has been advocated.

The author was able to save animals to which a lethal dose of Fowler's solution had been given by mouth or subcutaneously, by injecting full doses of **magnesium sulphate** hypodermically. Animals poisoned intravenously, however, could not thus be saved. D. Sieber (*Arch. Internat. de Pharm. et de Thérap.*, xxii, Nos. 3 and 4, 1913).

**Magnesium sulphate** prolonged the average life of a series of 50 rabbits poisoned by arsenic from 219 hours

to 415 hours on the average, but it did not prevent death. O. A. Hansen (*Jour. of Pharm. and Exper. Therap.*, Mar., 1921).

Experiments indicating that the "arsenic antidote" has no influence on poisoning by Fowler's solution. There is a slight, unimportant delay in the time of death from powdered arsenic trioxide, seemingly due to the colloidal nature of the antidote and delayed absorption. McGuigan, Atkinson and Brough (*Jour. of Pharm. and Exp. Therap.*, Apr., 1923).

The remaining measures to be used include **opium** to check vomiting and diarrhea, **saline hypodermoclysis** to make up for the fluid already lost and stimulate the renal eliminatory function, **demulcent drinks** to soothe the inflamed mucous membranes, and various stimulating remedies, such as **digitalis**, **strychnine**, **caffeine**, **camphor**, etc., together with **external heat**, in cases in the stage of collapse.

**CHRONIC ARSENIC POISONING.**—Symptoms of chronic arsenic poisoning may result either from the continued medicinal use of excessive doses of the drug or from its prolonged absorption through the lungs, skin, or alimentary tract by those whose work, food, or surroundings bring them more or less constantly under its influence. Workers in aniline dyes or copper occasionally show it. Wall-papers colored with arsenic formerly were responsible for many cases; the poison escaped into the atmosphere as a fine dust or vapor, but this danger has of late practically disappeared by reason of preventive legislation.

Epidemics of arsenic poisoning have occurred in England due to contaminated glucose used in the manufacture of beer. In Halifax an epidemic of arsenic poisoning was caused by the

use of malt which had been prepared with coke impregnated with arsenic.

According to Haywood and Warner, fixed compounds of arsenic in wall paper or fabrics may be so changed by the growth of molds that the arsenic is free and discharged in the atmosphere of rooms. In this way the inhabitants of rooms become the subjects of intoxication, usually manifested by supraorbital neuralgia, pain in the eyes, vague pains in the fronto-nasal region and in other parts of the body, restlessness at night, depression during the day, gastrointestinal disturbances, and slight fever. The most important symptoms are the orbital neuralgia and the lassitude. In rare cases skin eruptions, suppuration of the fingers, discharge from the ears, inflammation and ulceration of the ear passages, and other symptoms, have been observed.

Certain cosmetics containing arsenic, clothing fabrics and furs treated with it, as well as stuffed animals, have also given trouble. An epidemic of chronic arsenic poisoning occurred in England from the use of a beer in the preparation of which sulphuric acid containing arsenic as an impurity had been used.

A considerable degree of tolerance to arsenic may be acquired by continued oral use of gradually increasing doses. Thus, the so-called "arsenic eaters" among the peasants of Styria, in southern Austria, are said to be able to take doses of 8 grains (0.51 Gm.) of arsenic with impunity. It has been practically proven, however, by experiments in animals, that the supposed systemic tolerance is not present, but is merely simulated by a diminished power of absorption of the drug from the alimentary tract. Hypodermic injection of relatively small amounts of arsenic in animals habituated to it *per orem* caused death, as though no true general tolerance

had been acquired. It thus seems quite possible that where arsenic enters the system by being inhaled or absorbed through the skin, no pronounced degree of tolerance will be developed.

Besredka found that when a large non-lethal dose of arsenic is given to guinea-pigs, the leucocytes in the peritoneal fluid diminish greatly in number, the larger the dose the greater being the diminution. This lasts for ten or twelve hours, and is succeeded by great hyperleucocytosis. The animal is ill and out of sorts during this time, but in two or three days the blood becomes normal again, and vivacity and appetite are recovered. In the peritoneal exudation the phagocytic leucocytes take up the arsenic in small granules; the lymphocytes do not do so. During the diminution it is the former which disappear, while the latter persist. Phagocytic protection is also probable. EDITORS.

Starting with  $\frac{1}{60}$ -grain (0.001 Gm.) doses of arsenious oxide after meals, the writer gradually reached the dose of  $1\frac{1}{2}$  grains (0.078 Gm.), which produced irritability and distinct and lasting discomfort every way it was taken and all precautions notwithstanding. In 1-grain (0.065 Gm.) doses the drug could only be taken with comfort if dry foodstuffs were consumed at meals; if liquid beverages or soft foods were partaken of, the administration of the grain (0.065 Gm.) dose of  $\text{As}_2\text{O}_3$  produced immediate discomfort and burning pains in the abdomen, lasting 40 minutes to 1 hour followed by diarrhea. Harding (Lancet, Jan. 24, 1914).

The volatilization of solid arsenic in the human body, the cause of which is the "garlic breath" in arsenic eaters, probably takes place in the intestine as the result of the activities of certain bacteria, experiments having duplicated this behavior *in vitro*. A number of organisms seem to possess the power of transforming the arsenic into a gaseous form. Puntoni (Gaceta Med. Catalana; Med. Rec., Feb. 3, 1917).

The earlier symptoms of chronic arsenic poisoning vary somewhat according to the mode of introduction of the drug. Where it has been administered by mouth for therapeutic purposes, the first sign of poisoning is frequently a swollen condition of the eyelids, and puffiness below the eyes, which may be closely followed by congestion of the conjunctivæ and dryness, later increased secretory activity, of the nasal and pharyngeal membranes. Where the poison has been taken into the system by inhalation, frequently signs of bronchial irritation may be the first to appear. Another typical and early manifestation of chronic arsenic poisoning is disturbance of the gastrointestinal functions. The subject loses his appetite, complains of nausea, sometimes of vomiting and of pain in the stomach region, and of diarrhea.

Skin eruptions also occur very frequently; they may be of various types—erythematous, urticarial, papular, pustular, etc. More characteristic than these, however, are the modifications which take place in the superficial layers of the skin in long-standing cases. These consist chiefly of an overgrowth of the horny layer, especially on the palms and soles. There is at first, according to Jamieson, hyperidrosis of these areas, followed by the formation of warty corns around the orifices of the sweat-glands, and later a diffuse hyperkeratosis, associated with burning sensations. Finally, there results an exfoliation of scales from the epidermis. In prolonged cases of poisoning, loss of hair and of finger-nails may occur. In a few cases the liver is found enlarged; jaundice may be present. More frequently witnessed,

however, is a peculiar dark pigmentation of the skin—arsenic melanosis. Hutchinson reported a case in which, in addition, there were numerous large, black freckles on the face, while Foerster recorded that of a boy of 10 years who, upon taking 1 ounce of the liquor potassii arsenitis of the German Pharmacopeia in the course of two months, developed exophthalmos, thyroid pulsation, and a yellowish discoloration of the skin, face, and trunk, which gradually deepened into brown.

J. C. Muir has found that the blood of arsenical patients having deep cutaneous pigmentation is decidedly richer in red cells and hemoglobin than that of similar slightly pigmented or unpigmented cases. This, he maintains, disproves the almost universally accepted hypothesis that the pigmentation is due to destruction of hemoglobin or red cells, and is evidence for thinking that the melanin of the skin is an important element in the production of hemoglobin. The erythroblastic function of the marrow is more easily stimulated in the presence of a large store of cutaneous melanin.

Report of 4 cases of keratosis following the long-continued administration of arsenic, in 1 of which epithelioma of the finger supervened. The keratosis was of the circumscribed variety and affected the palms and soles, appearing as small, corn-like elevations. In 3 of the 4 cases it had been taken for psoriasis, in the one in which the epithelioma occurred for twenty years almost continuously. The microscopic changes consisted of circumscribed thickenings of the horny layer, atrophy of the derma, and complex alterations in the papillary layer. In no instance did he find any relation between the epidermal changes and the sweat-ducts.

The sequence of cancer is very exceptional, only 19 cases being on record, usually beginning many years after the initial keratosis had shown

itself, and sometimes when the drug had been stopped for many years previously. When epitheliomatous changes have taken place the course of the case is frequently rapidly malignant. Dubreuilh (*Annales de dermat. et de syph.*, No. 3, 1910).

Pigmentation of the oral mucous membrane observed in 2 cases. In the first, a woman aged 49 had been taking Fowler's solution for 6 years, to a total amount of 32,850 minims. In addition to extensive skin pigmentation and keratosis of the palms and soles, the oral and lingual mucosa was bluish throughout, with a deep blue area within the lower lip. In the second case, a man aged 57, with pernicious anemia, had taken 2400 minims of Fowler's solution in the course of a month. Two weeks after the onset of skin pigmentation, bluish discoloration appeared within the lower lip and cheeks; on making pressure around the patches to render them bloodless, a light-brown color replaced the blue. The hard palate showed a brown area. In some persons small amounts of arsenic suffice to produce untoward effects; pigmentation, keratosis and neuritis may appear in a few weeks. R. Stockman (*Brit. Med. Jour.*, Nov. 10, 1923).

Arsenic in the water may give rise to extreme cases of keratoderma. Córdoba province, Argentina, has several endemic foci of this condition. Endemic arsenicism is to be suspected where keratoderma is symmetric, and is certain if pigmentation is present in addition. The pigmentation persists longer than the keratoderma upon removal of the cause. J. J. Bosco (*Semana méd.*, Oct. 15, 1925).

Anemia is a common result of prolonged use of large amounts of arsenic.

Another important accompaniment of chronic arsenic poisoning is neuritis. This may occur also as a sequel to acute poisoning where the amount of arsenic absorbed is insufficient to cause death. It is more usually seen,

however, in the chronic type of poisoning, and is delayed until the drug has had opportunity to accumulate in the system for three or more weeks. The neuritis is typically multiple, and generally involves the limbs rather than the trunk. The earliest manifestation is often a sharp pain at one or more joints, together with headache, followed by disturbances of sensation such as hyperesthesia, itching, diminution or exaggeration of temperature sense, etc. The condition "erythromelalgia"—swelling, redness, and extreme sensitiveness to touch of the skin of a part—may appear.

Next comes paralysis of sensation, followed, in turn, by motor paralysis. The affection is usually symmetrical, and shows a predilection for the extensor muscles of the foot and the peronei in the lower limb, while in the upper extremity the extensor muscles in the forearm are chiefly involved. If the cause persists, atrophy of the muscles takes place, producing foot-drop and wrist-drop. Herpes zoster may be an accompaniment of the nervous involvement.

The writers call attention to disappearance of the Achilles tendon reflexes as an early sign of chronic arsenical poisoning in paretics subjected to intensive neoarsenobenzol treatment in the daily intravenous dose of 0.3 Gm. (5 grains), up to an aggregate dose of 12 Gm. (3 to 5 drams). The loss of the reflex indicates a latent arsenical neuritis of the internal popliteal nerve, unaccompanied by disturbances of locomotion, pain or muscular atrophy, yet already resulting in certain quantitative modifications of the electric reactions in the involved muscles. Paretics subjected to such treatment show marked physical and mental improvement, but there is no clinical or humoral

cure, the Bordet-Wassermann reaction in the cerebrospinal fluid persisting. Sicard and Roger (Paris méd., June 29, 1918).

Case in a girl of 14 who, after prolonged use of Fowler's solution for asthma, developed ascites, glycosuria, vomiting, brownish skin discoloration and loss of the patellar and Achilles reflexes. Operation and subsequent autopsy revealed partial bowel obstruction due to adhesive peritonitis, with hepatic cirrhosis. The adhesive peritonitis is ascribed to chronic arsenic poisoning. F. van Oppen (Nederl. Tijd. v. Gen., Sept. 15, 1923).

The 4th injection of sodium arsenate into the arm for slow convalescence from what had appeared to be influenza resulted in immediate and recurrent severe pain radiating to the hand, followed by typical radial paralysis with reaction of degeneration. Operation was undertaken, revealing a neuroma on the musculospiral nerve as it curved around the humerus. Two longitudinal incisions were made in the neuroma to afford an exit for the edema, and function returned almost completely thereafter. E. Strauss (Klin. Woch., June 24, 1924).

The final stage of chronic arsenic poisoning is characterized by mental apathy, anemia, emaciation, loss of the hair, salivation, and a tendency to hemorrhagic extravasations. Fatty degeneration in various viscera takes place, and death may occur from exhaustion.

The toxicity of arsenous oxide given undissolved by mouth varies markedly with the fineness of its subdivision. Toleration of large doses by mouth does not prove the existence of habituation, as it may be due to slow solubility and coarse subdivision of the drug. The doctrine of habituation to arsenic is open to question. There are no convincing reports as yet of habituation to arsenous oxide, whether given dissolved or undissolved. Schwartz (Jour. of Pharm. and Exp. Therap., Oct., 1922).

**DIAGNOSIS OF CHRONIC ARSENIC POISONING.**—This may be a matter of some difficulty, owing to the variety of the symptoms, and especially to the fact that the physician is apt to overlook the possibility of chronic arsenic intoxication because of its rarity.

In the event that there exists a history of taking the drug the diagnosis is of course plain. If such a history be not obtainable, however, a positive diagnosis will rest upon the chemical detection of arsenic in the urine.

Clinically, the conditions most readily confused with chronic arsenicalism are lead poisoning and alcoholic neuritis.

Lead paralysis is to be distinguished from that of arsenical neuritis by the blue line on the gums, the greater incidence in the upper limbs, the lack of involvement of the supinator longus and flexor muscles, and the constipation.

Paralysis of alcoholic causation may be differentiated by the characteristic facial appearance of the patient, the mental condition, and the history of an excessive indulgence in alcoholics.

Tabes dorsalis may be in certain respects simulated by chronic arsenic poisoning, but seldom closely enough to deceive.

Hyperesthesia of the skin and muscles, while not always absent in alcoholic neuritis, is much more consistent and generally severe in cases due to arsenic.

The vasomotor phenomena are also often very striking in the arsenical cases and very rarely present in the alcoholic. In one epidemic, ataxia was frequently noted in the arsenical cases,



while comparatively infrequent in the alcoholic. (Bury.)

The most convenient tests for arsenic in the urine are the following:—

1. *Reinsch's Test*.—This is made by adding to the urine, preferably already concentrated by boiling,  $\frac{1}{4}$  of its volume of hydrochloric acid and a bit of shining copper-foil. The mixture is boiled for some minutes, when, if arsenic be present, the copper will be observed to tarnish and darken in color to gray or black.

2. *Gudscit's Test*.—In a test-tube place a little metallic zinc, a few cubic centimeters of dilute hydrochloric acid, and a few drops of iodine solution; then add a few cubic centimeters of the urine. Promptly place over the orifice of the tube a cap of filter paper which has been moistened with a saturated solution of silver nitrate. In the presence of arsenic, a lemon-yellow color will appear on the filter paper, which will then turn black if a drop of water be placed on it. It is necessary, in performing this test, first to make sure that the reagents used do not contain arsenic; this may be done by placing the filter paper for a few minutes over the mouth of the tube before the urine has been introduced (Todd).

**TREATMENT OF CHRONIC ARSENIC POISONING.**—In addition to the removal of the patient from further contact with the drug, elimination of the arsenic already present in the system should be hastened by means of **potassium iodide**, **saline enteroclysis**, and **purgation**. The disturbances in the gastrointestinal tract should be treated with **bismuth**, **demulcents**, and other like **sedatives**. Plenty of good food should

be given to counteract the emaciation likely to be present. Arsenical neuritis, if it exists, may require **analgesics** at first; later, **massage** and **electric treatment** will be indicated to re-establish the function of the affected nerves and prevent muscular atrophy.

According to Bury, **warm fomentations** are useful in relieving the pain and **sodium salicylate** and **potassium iodide** are also of some service. **Strychnine** should not be given early in the affection.

**THERAPEUTICS. — Internal Uses.**—In certain anemias arsenic in moderate doses increases the number of erythrocytes, and is therefore especially useful in **progressive pernicious anemia** and in secondary anemias where the red-cell count is low. Unfortunately, its beneficial effect is generally not of long duration, a relapse usually taking place at a time when the prospects of recovery seem brightest. In **chlorosis** arsenic is ineffective when given alone, but assists the action of iron if administered in combination with it. In the several forms of **leukemia** and in **pseudoleukemia** arsenic is one of our most useful remedies, tending in many cases both to diminish the number of white cells and increase the erythrocytes; on the whole, however, the results are even less to be depended upon than in the progressive pernicious type of anemia. The most convenient method of prescribing arsenic in these cases is to give Fowler's solution internally, beginning with doses of 2 minims (0.12 c.c.) after each meal and increasing by 1 minim (0.06 c.c.) every day, provided no untoward effects appear, until 15 or 20 minims (0.9 to 1.2 c.c.) are being

taken. The medication should be intermitted for a week at rather frequent intervals in order to avoid excessive storage in the viscera.

In various **cachectic conditions** arsenic not only tends to improve the condition of the blood, but exerts a very favorable effect upon the general nutritive state by virtue of its so-called "alterative" action. Thus, in the cachexia of **chronic malaria**, especially in cases where the specific effect of quinine has worn off, arsenic in the form of ascending doses of Fowler's solution or the trioxide is a remedy of acknowledged worth. In the neuralgic paroxysms of masked intermittent fever, arsenic is also often of great value. Its effect may oftentimes be enhanced by combination with iron and quinine. As a rule, full doses of arsenic are required in malaria. Where, after a time, the stomach rebels under it, the hypodermic method of administration should be resorted to. According to Downie, arsenic is valuable as a prophylactic against malaria. Some authors counsel the administration of arsenic and iron in ordinary cases of intermittent fever, after the paroxysms have been subdued with quinine.

The progress of malignant tumors such as **epithelioma** and **sarcoma** is sometimes retarded by the internal administration of arsenic. Koenigsberg reported a case of sarcoma of the head of the tibia which he claimed had recovered through the influence of this remedy. It is well known, too, that various forms of **verruca**, including the common wart, are sometimes caused rapidly to disappear by arsenic, given in conjunction with external treatment; the use of the drug is especially advantageous where multiple

lesions are present. Müller recommends for children Fowler's solution in the commencing dose of  $\frac{1}{4}$  minim three times a day, gradually increased.

In the various painful neuroses included under the name **gastralgia**, Sawyer strongly recommends the trial of arsenic trioxide in  $\frac{1}{24}$ -grain (0.0027 Gm.) doses, given in a pill with 2 or 3 grains (0.13 to 0.2 Gm.) of extract of gentian three times daily, midway between meals. In cases of moderate severity, according to this author, no other treatment is needed, though in more pronounced cases, counterirritation to the epigastrium should be used in addition. A varied dietary should at the same time be prescribed, and the arsenic continued for some weeks.

In **diabetes mellitus** arsenic is sometimes of service. Forchheimer preferred it to opium in this affection and recommended that it be given in the form of Fowler's solution in ascending doses until mild toxic effects were produced, when the dose was to be gradually diminished. It has been especially advocated in the severe cases, in combination with the usual measures, and is deemed valuable in neurotic, debilitated subjects. Forchheimer found that repeated courses of arsenic did not lose their effect in diminishing the glycosuria and the production of acetone bodies.

In **bronchial asthma** arsenic is not infrequently a useful remedy for continuous administration in the intervals between paroxysms. The best results, it has been asserted, are obtained in the young. Arsenic may also with advantage be added in the cigarettes of stramonium and hyoscyamus leaves often used in this affection. Prevailing views as to the action of arsenic offer no definite clue as to the manner in

which the drug exerts its effects in asthma.

The same is true of the use of arsenic in the **vomiting of pregnancy**, as recommended by Auldc, who prescribes it in the following combination:—

**R** *Arseni trioxidi*,  
*Ext. ignatiæ*,  
 of each ..... gr. ss (0.03 Gm.).  
*Pulv. ipecacuanhæ*,  
*Ext. cascara sag-*  
*rada*.....of each gr. xv (100 Gm.).  
*Olei gaultheriæ*, .. mij (0.12 c.c.).

M. et ft. in pil. no. xx.

Sig.: One pill after meals.

The patient should be advised to restrict the use of fluids at meals, and drink principally between meal hours.

The favorable influence of arsenic upon nutrition also renders it useful in **pulmonary tuberculosis**. Bonney finds that through its employment a marked improvement in the appetite sometimes occurs. He advises the use of 1 minim (0.06 c.c.) of Fowler's solution three times daily as an initial dose, cautiously increased to 5 minims (0.3 c.c.). The preparation should be given in a half-glassful of water after meals, and may, if desired, be combined with strychnine. After two months its administration should, as a rule, be stopped, at least for a time. Arsenic has been credited by some with the power of arresting night-sweats in phthisis.

In **rickets** small doses of arsenic have sometimes proven of great value.

In **arthritis deformans** arsenic is among the drugs which, if given early in the disease, do the most good. It may with advantage be alternated with iron, and should be administered for some months after the preliminary acute manifestations have disappeared.

In the treatment of certain **nervous**

**conditions**, especially **chorea** and **neuralgias**, arsenic has a well-deserved reputation. In the former affection it should be given in rapidly ascending doses until, in a child 10 years old, *e.g.*, 35 minims (2.1 c.c.) of Fowler's solution are being taken daily, or vomiting appears. If no untoward effect shows itself, the amount given should be gradually decreased. In chronic choreic cases large doses often prove very effective where smaller ones have already been found useless. The drug should be given after food, and the little patient required to lie down for a half-hour afterward in order to avoid nausea and vomiting.

The writer's experience sustains the view that minute, long-continued doses of arsenic exert a stimulating action on nerve tissue. The benefit was marked in 8 out of 12 cases of **multiple sclerosis** in his experience. The improvement was at first mostly subjective, the patients gaining in weight and feeling better generally, and this was soon followed by better functioning of the legs, some patients even being able to take long walks, when before they could not even stand without assistance. The best results were obtained in cases of uncomplicated multiple sclerosis in which the optic nerve was still intact. H. Willige (Münch. med. Woch., Mar. 22, 1910).

In many **chronic skin diseases** arsenic is a most valuable remedy, though in acute cutaneous conditions it is, on the contrary, harmful. It is conceded to improve in some way the nutrition of the superficial layers of the skin. **Psoriasis** is in many instances considerably benefited by Fowler's solution, given in doses of 3 to 5 minims (0.18 to 0.3 c.c.) in water after meals, slowly increased until the maximum of benefit is obtained or the limit of tolerance is

reached. According to several authors, the solution of sodium arsenate is better borne in patients with sensitive digestive tracts than Fowler's solution, and should, therefore, be given the preference over it. It has also been suggested that in robust, plethoric patients exhibiting lesions of distinctly inflammatory aspect, liquor potassii hydroxidi, in doses of 10 to 30 minims (0.6 to 1.8 c.c.), be given in combination with the arsenic preparation. It has been recommended to begin the arsenic treatment in psoriasis with a saline diuretic such as potassium acetate or bitartrate. In rebellious cases of the disease, or where prompt effects are particularly desired, hypodermic injections of Fowler's solution or of sodium cacodylate may be given. Herxheimer gave intravenous injections of arsenic trioxide in 25 cases of psoriasis, in doses ascending from  $\frac{1}{60}$  grain (0.001 Gm.) to  $\frac{1}{4}$  grain (0.016 Gm.); 10 cases were completely cured, 6 much relieved, and 9 reported as still under treatment, but greatly improved.

In some cases of **chronic eczema**, where moisture is absent from the lesions, and the latter are chiefly papular and scaly, arsenic is to be remembered as of possible benefit; it is not by any means so dependable, however, as in psoriasis, and in some cases in which it is tried may have to be given up because of aggravation.

In **acne** of the slowly evolving papular type, especially where anemia is present in addition, arsenic often proves effective, though the digestion may be disturbed by it if it is not cautiously used. In more acute types it is apt to do more harm than good.

Other skin diseases in which arsenic has proved of special value are

**pemphigus** (in which it should be given for a prolonged period in gradually increasing doses), **lichen planus**, **dermatitis herpetiformis**, and **alopecia areata**. It may also, though less often, prove beneficial in resistant cases of **seborrhea** and **chronic urticaria**.

It may be generally stated that arsenic is a drug of undoubted value in a limited number of skin diseases, especially in **psoriasis**, **lichen planus**, and **acute pemphigus**. It is useful in the quiescent stages of the first two diseases when the active inflammatory symptoms have subsided. Even when used in appropriate cases and at the proper stage, it often fails lamentably.

Arsenic is excessively and indiscriminately prescribed by practitioners in the treatment of skin diseases. It is a potent drug exercising a stimulating and later on irritative influence upon nerve structure. It should not be given unless there is a good reason, and patients must not continue it upon their own judgment. Schamberg (*Therap. Gaz.*, June, 1908).

While arsenic cancer of medicinal origin is well known, little attention has been paid to cases of industrial origin, although their occurrence was known as long ago as 1820. The writer records 1 case and abstracts 2 others from the records of the London Hospital. All 3 men were engaged in the manufacture of sheep-dip—an arsenite of sodium containing arsenic sulphide and free arsenous oxide. The process of manufacture is very dusty. The clinical picture comprises pigmentation, keratoses and single or multiple squamous carcinomata. W. J. O'Donovan (*Brit. Jour. of Derm.*, Nov., 1924).

[The production of cancer through the injudicious use of arsenic recalls a series of cases of arsenical cancer described by Mr. Jonathan Hutchinson many years ago: 1. A man, aged 35, had keratosis of the palms and had three growths excised from different parts in 7 years. 2. A man, aged 46, was emaciated and very ill. Cancer developed in an old psoriasis patch

on the abdomen and also on the back. His hands became harsh and dry, but corns did not form. He had taken arsenic since the age of 14. 3. A lady had taken arsenic for long periods for lupus. In December, 1888, her palms and soles were in a condition of keratosis and arsenic was forbidden. In July, 1890, the palms and soles had recovered. At one time in 1877, while taking arsenic, the edge of the lupus patch assumed the hard-rolled condition of rodent ulcer. 4. A lady, aged 45, who for a long time had keratosis of the palms, had a squamous-celled epithelioma of the neck as big as a child's fist. Thickened, ulcerated skin had twice been excised from her palms. The interval between the date of suspension of arsenic and the development of keratosis may be prolonged over many years. In 1 typical case of arsenical cancer the arsenic was taken in early life and the cancer did not develop until senility. En.]

In the treatment of **psoriasis**, arsenic seems to do best in recent cases and such as have not had other arsenical treatment. In **lichen planus** it is generally admitted to be a useful remedy. It is most effective when the eruption occurs in limited areas and when there is little or no itching. If the greater part of the skin is involved and there is marked pruritus, it is apt to aggravate the latter and seems to influence the course of the disease but little. In such cases other remedies, such as the salicylates, will be found more useful. In **pemphigus**, while hardly a specific or even curative, it is one of the most useful internal remedies, diminishing the liability to relapse and lengthening the intervals between the outbreaks. Much the same can be said as regards its value in **dermatitis herpetiformis**.

There is considerable evidence that arsenic, especially when given hypodermically, is sometimes useful in **sarcoma** of the skin, and more particularly in the form described by Kaposi as "idiopathic multiple hemorrhagic sarcoma." The writer has seen an apparent arrest of the disease under its influence. In a small

number of cases arsenical treatment has appeared to be useful in **mycosis fungoides**, but, in the opinion of most authors, little is to be expected from it in the majority of cases. M. B. Hartzell (Jour. Amer. Med. Assoc., Oct. 31, 1908).

It is in the patients who have suffered from psoriasis that epitheliomatous developments due to arsenic have most frequently been recorded. Some 30 cases are now on record. The writer describes a case of his own in a woman. In spite of operative removal, death occurred, apparently from internal metastatic growths, about 2 years after the first came under medical treatment. R. Pye-Smith (Lancet, July 19, 1913).

From 1885 to 1912 only 15 cases of arsenical cancer have been reported out of hundreds who have been taking arsenic for long periods without getting cancer. The total number of cases is insignificant and negligible compared with the number of those taking arsenic for various diseases, habitual caters, and the total incidence of cancer. The right clue is to be found in the local applications. The occurrence of cancer 10, 20, or 30 years after discontinuing the internal use of arsenic is due to abnormal cell proliferation induced by the external application of chrysarobin, pyrogallol, tar, and other chemical irritants to patches of psoriasis for several years, before, during, and after the internal use of arsenic. The same is true in cancer occurring upon lupus vulgaris, lupus erythematosus, and syphilis. Keratoses and warts, whether due to arsenic or to other causes, have a tendency to undergo cancerous degenerations when subject to chronic irritation and injury, but there is no special liability where arsenic has been given internally for a long time. Arsenic is only responsible for the production of the keratotic condition, or preparation of the favorable soil, but the development of cancer is quite independent of arsenic. C. E. de Silva (Med. Press, Mar. 27, 1918).

In certain constitutional diseases, due to animal parasites, other than malaria, which has already been mentioned, arsenic has an important field of use. In **trypanosomiasis** it has been found appreciably effective, and is administered chiefly in the form of atoxyl (*q.v.*). For information concerning the organic arsenic preparations employed in **sypilis**, the reader is referred to the heading Dioxidi-amidoarsenobenzol.

Donovan's solution (liquor arseni et hydrargyri iodidi) has been extensively employed in the anemia of sypilis, and combines the beneficial influences of 3 of the remedies of greatest value in this affection.

In cases of **sypilis** which no longer respond to mercury, the writer has used successfully a solution of arsenic which consists of 1 Gm. (15 grains) arsenic trioxide and 2.25 c.c. (36 minims) normal soda solution in 100 c.c. (3½ ounces) of distilled water, representing a 1 per cent. solution of sodium arsenite, a solution which is very slightly alkaline. Its hypodermic use does not cause more inconvenience than an injection of morphine, while its intramuscular injection is painless. Hertzfeld (Jour. Amer. Med. Assoc., Feb. 25, 1911).

In **anemia** subcutaneous administration of arsenic is most effective, but as the injection of sodium arsenate—2 to 10 mgm. ( $\frac{1}{32}$  to  $\frac{1}{8}$  grain) at a dose—is painful, sodium cacodylate is preferred, being given in alternately increasing and decreasing doses: 0.01 Gm. ( $\frac{1}{80}$  grain), 0.1 Gm. ( $\frac{1}{2}$  grains), 0.01 Gm., and 0.1 Gm. For internal use a solution of potassium arsenate is recommended, 2 to 10 drops 3 times daily in ascending, then descending doses, for 6 weeks. A combination of iron and arsenic is practicable in the form of tincture of iron arsenate (liquor potassii arsenitis and tinctura ferri pomati in equal parts) or of pills of iron arsenate each containing

1 mgm. ( $\frac{1}{60}$  grain) of arsenic and 0.06 Gm. (1 grain) of iron. F. Müller (Deut. med. Woch., June 23, 1922).

Intravenous use of arsenicals, such as neoarsphenamin, in **ulcerative stomatitis** recommended on the basis of experience in 25 cases. Improvement began, on an average, 2½ days after injection and cure was complete within 6 days. Local application of *Bowman's solution* (Fowler's solution and wine of ipecac, of each 12 c.c., and glycerin, 8 c.c.) to the gums was effective, but relief was not always permanent. In 8 cases the 2 procedures were used simultaneously, but the period of cure was no shorter than after intravenous injection alone. E. A. Morgan (Amer. Jour. Dis. of Childr., May, 1923).

Another therapeutic use of arsenic was introduced by Lombroso as a result of studies conducted by Coletti and Perugini, *viz.*, in **pellagra**. Though it cannot be regarded as a specific, it is nevertheless efficient in many cases.

Lombroso used it in the form of Fowler's solution in dosage of 5, 10, 15, 20, and 30 drops (0.3, 0.6, 0.9, 1.2, 1.8 c.c.), or in the form of pure arsenous acid (arsenic trioxide) dissolved in slightly alcoholized water, in doses of  $\frac{1}{40}$  to  $\frac{1}{20}$  mg. ( $\frac{1}{2560}$  to  $\frac{1}{280}$  gr.), increasing, according to tolerance, up to 0.001, 0.002, or 0.003 grams ( $\frac{1}{40}$ ,  $\frac{1}{32}$ ,  $\frac{1}{20}$  gr.) and very rarely even to 0.01 gram ( $\frac{1}{8}$  gr.). The administration of the drug is suspended for a few days from time to time. C. H. Lavinder (Public Health Reports, Sept. 10, 1909).

The majority of cases of **pellagra** will at some time or other be benefited by arsenic. In the earlier stages the writer has had the best results with soamin administered hypodermically, starting with 1-grain (0.065 Gm.) doses every other day and increasing up to 3 or more grains (0.2 Gm.) to the dose until from 75 to 100 grains (4.8 to 6.5 Gm.) have been given, followed by a period of rest for a couple of weeks, then another

course of the drug if necessary. For internal use he believes Donovan's solution to give results slightly superior to those of Fowler's solution. The method recommended by Babes, of using atoxyl hypodermically, arsenic trioxide internally in  $\frac{1}{30}$ -grain (0.0022 Gm.) doses, and about 1 dram (4 Gm.) of a 2 per cent. arsenic trioxide ointment rubbed into the skin, would seem valuable in the early stages. Louis Leroy (*Southern Med. Jour.*, Mar., 1912).

Case of **pellagra** with rapid recovery under treatment by a generous meat diet and sodium cacodylate intravenously. The patient was a woman of 50, and the case was of interest in that she resided in South Dakota, a supposedly non-pellagrous territory. She had been deprived of meat for about 2 years prior to the onset of the symptoms. G. D. Head (*Arch. of Int. Med.*, July, 1924).

**External Uses.**—The slow caustic action of arsenic has led to its free use for the eradication of superficial malignant growths such as **epithelioma**. Where the growths are superficial and indefinite in their outline, many dermatologists have countenanced the use of caustics, of which arsenic is among the most useful because it possesses to a certain extent the property of sparing normal tissues and limiting its effects to the morbid cells. Thus, the application of Marsden's paste, consisting of 2 parts of arsenic trioxide to 1 part of mucilage of acacia, or of a mixture of the same ingredients in different proportions, has generally been followed with the desired result. A layer of paste being applied over the growth, a piece of dry lint is placed over it, overlapping the paste one-half inch all around. After ten minutes the overlapping lint is carefully cut away and the paste is allowed to dry. After two or three days poultices are

applied at short intervals until the redness and swelling present subside. A line of demarcation appears around the lesion, the skin ulcerates, and the fissure formed gradually extends until the epitheliomatous mass comes away. The result of the caustic treatment with arsenic is obtained more slowly than with other agents such as potassium hydroxide, and the pain is more prolonged, if less acute. Cases of poisoning due to its absorption from the skin have been reported, but the danger is not such as to interfere with its careful use.

Morphine and cocaine have been of only slight assistance in controlling the pain caused by arsenical paste in the treatment of **cancer**. The writer has found in orthoform a means by which the pain can be obviated. Equal parts of arsenic trioxide, gum acacia, and orthoform made into a paste are applied. The anesthetic influence of the orthoform lasts several hours, and the action of the arsenic trioxide is in this way rendered painless. W. P. Nicholson (*Atlanta Jour.-Rec. of Med.*, vol. i, p. 738).

Another efficient, though somewhat more troublesome, method of using arsenic is that of Czerny, who applies a solution of 1 part of arsenic trioxide in 150 parts of a mixture of alcohol and water in equal amounts. The first step in the treatment is thoroughly to cleanse the sore by vigorous rubbing or scrubbing, causing a moderate amount of hemorrhage. The surface is then well moistened with the solution,—previously shaken up,—and the preparation allowed to dry, preferably without dressing of any kind. A scab forms, over which the solution is applied daily, until the former loosens and is retained in place only by a few loose adhesions. These are divided, the scab removed, and a fresh application of the arsenical

solution made. If on the next day the resulting scab is thin, light yellow, and easily detachable, this indicates that the tissues no longer comprise any trace of cancerous growth. If, on the other hand, a dark-colored, firm and closely adherent scab again forms, the treatment must be repeated. The thicker the scab, the stronger the solution should be made for the second treatment, *e.g.*, 1 to 100 or even 1 to 80.

It should be noted that with cancer pastes some of the deeper tumor cells may escape destruction, recurrence resulting. The method is, in general, inferior to surgery or radiotherapy.

L. T. DE M. SAJOUS,  
Philadelphia.

**ARSPHENAMIN.** See DIOXY-DIAMIDOARSENOBENZOL.

**ARTERIAL PRESSURE AND BLOOD-PRESSURE.** See BLOOD-PRESSURE.

**ARTERIOSCLEROSIS.**—**SYNONYMS:** *Atherosclerosis; Chronic Arteritis; Hardening of the Arteries.* Progress in our knowledge of this disease has been very slow. This is due to neglect of the functions of the ductless glands. Particularly does this apply to the rôle I had found the adrenals to fulfill in tissue oxidation and thermogenesis, hemolysis and autolysis, the latter condition being the dominant factor of the lesions of which the arterial system is the familiar seat.

The etiology of arteriosclerosis is abundantly discussed in medical literature but most authorities agree that our knowledge is still limited and uncertain. Mortensen (*Jour. Amer. Med. Assoc.*, Nov. 28, 1925).

In view of the fact that arteriosclerosis, with its many cardiac, cerebral,

and renal complications, has become the deadliest of human affections, it was deemed advisable to treat the subject on neglected lines, *i.e.*, with the various ductless glands involved as participants in the pathogenesis of the disease, as I interpret their functions. Hence the following personal definition.

**DEFINITION.**—Arteriosclerosis may be divided into three dominant forms: 1. The *senile*, due to declining functional activity of the endocrine organs which sustain thermogenesis and the vital process, including that of the arteries; 2, the *autolytic*, due to the presence in the blood of endogenous or exogenous poisons which cause the immunizing constituents of the blood to include the vascular tissues in their hydrolytic action and give rise to local atheroma or sclerosis; 3, the *hyper-adrenic*, due to excessive activity of the adrenals, characterized by autolytic lesions in the middle coat of arteries, especially those of the extremities, as a result of excessive physical labor or muscular fatigue.

**PATHOGENESIS.**—The term "arteriosclerosis," introduced by Lobstein in 1831, means strictly what he intended it to portray: "a hardening and thickening of the arteries." In truth, this definition represents only, in the light of modern pathology, the results of advanced changes, but affords no clue to causal factors or the nature of morbid processes which lead to this degenerated state of the arteries or to its symptomatology. As it stands, the term arteriosclerosis is applied to practically any lesion which may compromise the integrity of the vascular walls chronically. This state of things has not only entailed confusion, but has made it impossible to



interpret or treat the morbid process intelligently, despite the vast amount of labor devoted to the question as a whole.

The importance of arteriosclerosis in the clinical domain asserts itself when we realize that it is directly and indirectly the major cause of death of our day, owing to its fundamental connection with various cardiac disorders, angina pectoris, aneurism, apoplexy, general paresis, etc. As Huchard well said, arteriosclerosis is in reality not a disease but a "family of diseases." Hence the many difficulties which have militated against its proper interpretation and treatment, thus perpetuating its death-dealing attributes.

The fundamental cause of the generally recognized confusion which has hampered progress in the study of arteriosclerosis, however, has been neglect, until recently, of the dominant rôle of biochemistry in its pathogenesis. Particularly does this apply to a class of fat-like bodies termed lipoids or lipins. Prominent among these are *lecithin*, first isolated by Gobley, a French pharmacist, in 1845, and *cholesterin*, or better, *cholesterol*, first isolated from gall-stones by the French chemist, Fourcroy. Despite the imposing array of researches devoted to these lipoids, and their known presence in all tissues, a leading authority on the subject, Hugh MacLean, recognized as late as 1918 that "the special part played by lipins [lipoids] in the activity of the organism is entirely unknown to us." In 1923 my own labors, based on the all-science method, enabled me to point out that both *lecithin* and *cholesterol* were active factors in tissue respiration and metabolic processes—an

amplification of previous work published in 1903 and 1917, in which I showed that *lecithin* and *cholesterin*, familiar constituents of all nervous tissues, took part in the metabolic functions of these tissues, including the brain and spinal cord.

To interpret arteriosclerosis in the light of modern research, therefore, it was deemed necessary to review briefly the prevailing knowledge concerning the lipoids mentioned, my interpretation of the functions which they carry on in the tissues, and the manner in which they take part in the pathogenesis of this vascular disease.

**LECITHIN.**—Phosphorus, the dominant element of *lecithin*, which occurs in this waxy yellowish substance in the proportion of 3.95 per cent. (Thierfelder), plays a leading rôle in metabolism, and those tissues which are richest in this element are known to be the most active. Thus, the nuclei and nucleoli of animal and plant cells, brain, nerves, roe, egg yolk, sperm, the electric organs of fishes, pus, milk, muscles, blood corpuscles and plasma, lymph and bile all contain a relatively large proportion of phosphorus. As far back as 1812, Vauquelin, a French chemist, had found that brain tissue contained phosphorus, forming part, as later shown by Gobley (1845), of what the latter termed "*lecithin*," from the Greek "*lekithos*," meaning egg-yolk. In the brain *lecithin*, however, the proportion of phosphorus is slightly greater than elsewhere, being 4 per cent. (Thudicum) and is known as "*kephalin*." In the heart muscle, also rich in *lecithin*, the latter is termed "*cuorin*." There is no difference in the phosphorus content, the only warranty for the different term being a

slight difference in the carbon and nitrogen values. As far as the pathogenesis and treatment of arteriosclerosis are concerned, however, the only facts which require emphasis are that the brain lecithin is slightly richer in phosphorus than is that of the body at large and that the cerebral vessels are correspondingly more vulnerable to pathologic changes.

Of importance also is the intimacy between lecithin and all living substances. It occurs in close association with the cellular proteins and fats. The tenacity with which it combines with them is such that it is preserved even during extreme emaciation. The reason for this becomes plain in the light of my own labors, as we shall see presently. Briefly, I regard lecithin and its isomers as the fuel of the organism, the coal in the furnace of life, but also, in the present connection, as fuel capable of destroying both tissues and life when the heat that it can liberate becomes excessive through injudicious activation.

**CHOLESTEROL.**—Although, as we have seen, Fourcroy first isolated cholesterin from gall-stones, the first complete study of this substance was published by the French chemist, Chevreul, who gave it its former name "cholesterin" in 1814. Unlike lecithin it contains no phosphorus and is in fact a monatomic alcohol; hence the term "cholesterol" bestowed upon it in recent years. It has also been shown to be a constituent of practically all tissues and fluids of the body, and occurs likewise in plants (phytocholesterin). Like lecithin, it is especially abundant, however, in the white matter of nervous tissues, the brain, cord and nerves, the adrenals, the red corpuscles, and tissue rich in fats, the

bone marrow, the subcutaneous tissues, the peritoneum, etc., invariably accompanying their lecithin. It is also present, similarly combined, in all muscles, including those of the cardiovascular system. It is likewise found in pathologic products, pus, certain biliary calculi and exudates, pericardial, peritoneal, scrotal, etc.

The physiologic rôle of cholesterol has been variously regarded as anti-toxic, bactericidal and antihemolytic, but the comprehensive researches of Linossier (1920) have conclusively shown that its supposed antitoxic rôle was due to a misinterpretation of the functions of lecithin, and that laboratory and clinical findings also prove that cholesterol acts in the body as an antihemolytic. He recalled that while phospholipoids, which include lecithin, rendered the red corpuscles vulnerable to the hemolytic effects of venoms, cholesterol protected these cells against this destructive process. Clinical experience with cholesterol in the treatment of pernicious anemia, cancer, etc., fully sustains this interpretation.

An explanation of the manner in which this antihemolytic process is carried out has, however, remained obscure. It is this phase of the process, which is essential in the study of arteriosclerosis, that my own labors have tended to elucidate.

**THE LIPOIDS AS THERMOGENIC AGENTS.**—We have seen in the section on ANIMAL EXTRACTS, in the first volume, that I attribute to lecithin and cholesterol a function which had remained obscure ever since the discovery of oxygen, that of *heat production* or *thermogenesis*. Even to this day Howell, for instance, states in his text-book of physiology (1924 edition)

that "the respiratory history of oxygen ceases after this element reaches the tissues"—a fact which fully warranted Halliburton's statement in the 1921 edition of his text-book on the same subject that "knowledge of tissue respiration is so scanty that we can say but little of its pathological bearing." Conversely, I have adduced conclusive evidence (see *Endocrinology*, Nov.-Dec., 1925, p. 442) to the effect that the adrenals were the organs which carried on this all-important function.

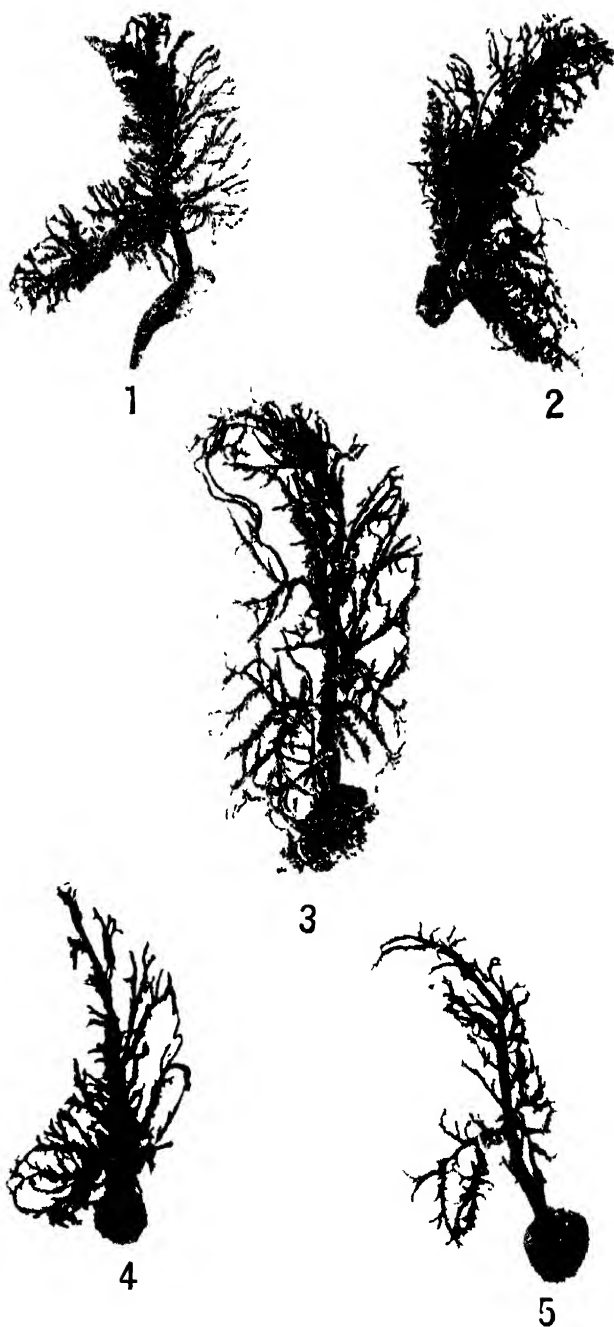
The rôle of lecithin and cholesterol in tissue oxidation, as I described it, may be summarized as follows: Of the two lipoids which the adrenal cortex is known to contain, the one, the *phospholipoid* lecithin, when oxidized by tissue *oxygen*, liberates the systemic heat energy, the interaction of phosphorus and oxygen, as is well known, developing *heat*. The lecithin phosphorus needs, however, to be controlled; otherwise it would develop an excess of heat energy and cause tissue necrosis. The controlling or inhibiting agent in this connection is the *cholesterol*, which acts by moderating or lowering the lability of the lecithin phosphorus to oxygenation. This would seem to leave the thyroid hormone out of consideration; but such is not the case. While cholesterol *inhibits* oxidation of lecithin the organic iodine of the thyroid secretion *accelerates* this process by increasing the lability of the lecithin phosphorus, and thus raises the basal metabolic rate. Briefly, lecithin, the systemic thermogen, is so stimulated physically by the thyroid hormone (thyroidase or thyroxin) and restrained by cholesterol as to maintain normally a mean temperature of 98.6° F. (37° C.) and

a basal metabolic rate of approximately 100 per cent.

What is the bearing of this thermogenic process upon the pathogenesis of arteriosclerosis? Cholesterol restraining the thermogenic action of lecithin, we shall now see that its anti-hemolytic activity is due to this property through a corresponding inhibition of the proteolytic action of enzymes.

**THERMOGENIC ACTIVATION OF TISSUE ENZYMES.**—As Vaughan has well said, "the cell which can no longer supply a digestive ferment is already dead," and its "general trend of action," as Chittenden expressed it, "is hydrolytic cleavage." In other words, precisely as is the case with the digestive ferment, or better, enzyme, trypsin in the intestine, so does the trypsin in all living cells carry on a digestive process by hydrolysis. An essential feature in the present connection, however, is that the digestive or hydrolytic activity of trypsin is marked according to the heat to which it is subjected. Thus, while it splits proteins, tissue elements of food, etc., under normal conditions at the body temperature of 98.6° F. (37° C.), it does so with increasing rapidity as the temperature is raised until 104° F. (40° C.) is reached (Hammarsten).

Applying this principle to the pathogenesis of arteriosclerosis, it will become apparent that the arterial lesions are due to excessive tryptic activity. Thus, we have seen that the phospholipoid lecithin, oxidized by the oxidizing enzyme adrenoxidase, serves to liberate heat energy, and that this property is regulated by the cholesterol and the thyroid hormone—all constituents of the tissue cell. If the lecithin is given a free hand by diminution of the cholesterol-restraining influence,



THE ADRENAL VESSELS IN THE YOUNG AND OLD.

1. Man, 22 years old    2. Woman, 30 years old.    3. Pregnant woman, 22 years old.  
4. Man, 80 years old.    5. Woman, 82 years old    (*Landau.*)

From Sajous, "Internal Secretions," Vol. I.



the temperature is allowed to rise and the hydrolytic activity of the tissue trypsin is increased, provoking the condition we term *fever*. If the process becomes abnormally active the red corpuscles are subjected to the hydrolytic process in the liver, especially where the temperature is higher than elsewhere in the body, thus causing *hemolysis*. If the hydrolytic process is rendered still more active, the tissue cells, those of the arteries particularly, are also more or less involved in the destructive process, *i.e.*, subjected to *autolysis*.

Arteriosclerosis, in which autolysis is a dominant factor, thus becomes, from my viewpoint, one of the sequences of this destructive process, the areas of sclerosis acting as obturators of threatening perforative lesions, and calculated, therefore, to preserve as far as possible the integrity of the vascular walls and the patency of the diseased vessels as blood channels.

**PATHOLOGY.**—An important feature in this connection is the recognition of three distinct types of arteriosclerosis, accepting this term only as a convenient one to indicate hardening of the arteries as a cause of deficient contractile power, general or local.

**SENILE ARTERIOSCLEROSIS.**—Advancing age produces changes in the vessels irrespective of any clearly defined pathological factors; hence the above name which implies a normal condition. A plate is submitted on the opposite page in which the degenerative influence of senility on these organs is strikingly shown.

Senility, however may occur at any age, *e.g.*, in the young and middle age, from premature tissue wear. It affects particularly the middle coat or

tunica media, which is composed of two circular layers, one of elastic tissue and the other of unstriated muscle tissue disposed crosswise alternately. But these tissues suffer from chemical deterioration incident upon premature decay. The elastic tissue loses its elasticity and tends to become dry and brittle. The muscular tissue, being composed of unstriated muscle fibers, is dominated chemically by the medullary product of the adrenals. This middle coat, or contractile muscular layer, thus becomes more or less rigid and fails correspondingly to assist in the propulsion of the cardiac wave. The arterioles or small terminal arteries which do not contain elastic fibers suffer similarly from the diminution of the adrenal hormone which, with their sympathetic supply, subserves their contractile functions.

Arteriosclerosis resulting from thyroid deficiency is stressed by the writer. In myxedema there are well-marked arterial changes, and many cases develop the typical picture of hypertension with resulting myocardial insufficiency and cerebral hemorrhage. The necropsies before the introduction of thyroid treatment showed in the majority of cases marked arteriosclerosis and chronic interstitial nephritis. In the writer's case of thyroid atrophy there was hypertension with sclerosis both of the larger vessels and the arterioles in various organs. A. M. Fishberg (Jour. Amer. Med. Assoc., Feb. 9, 1924).

In this senile form of arteriosclerosis the specific lesions of the disease, nodules in the internal coat or *intima* and the sclerosis and calcification found in the external coat or *adventitia*, are sometimes entirely missed, their presence betokening a pathogenicity superadded to that due to progressive old age.

The claim that an inherent weakness of the arterial wall existing in the individual from the time of birth is an important factor in the subsequent sclerosis cannot be proved either in clinical or pathological study. Osler laid some stress upon this point, believing that the elements entering into the structure of an artery may be "shoddy" as regards their strength in dealing with the circulation. But it is difficult to determine the character of this "shoddy" structure. O. Klotz (*Annals of Clin. Med.*, Apr. 1926).

#### **AUTOLYTIC ARTERIOSCLEROSIS.**

—It is in this form that the autolytic or digestive process previously described, in which lecithin, cholesterol, trypsin and other agents take part, prevails. Through the agency of some pathogenic agent, a toxic waste product, more or less virulent organisms or their toxins, inorganic poisons, etc., to be enumerated under the next heading, the autolytic or digestive action of the tissue trypsin is raised beyond the needs of cellular life by the extra-physiological heat liberated by the interaction of the lecithin and oxidizing agent adrenoxidase—all activated by an undue production of the thyroid hormone thyroiodase. This, in truth, constitutes a defensive reaction, general and local, whose purpose is to counteract the harmful factor, but in which the overactive trypsin, rendered so by an excessive liberation of heat by the oxidized lecithin, not only hydrolyzes or digests the pathogenic agent, but also the tissues in which the latter occurs or is embedded. A corresponding number of areas of focal ulceration or necrosis are thus formed, the inhibitory influence of the cholesterol having proven inadequate to control the abnormal thermogenic activity of the lecithin.

Both external and middle coats may

be the seat of such lesions, owing to the presence of the pathogenic organisms in aggregates more or less compact numerically. Where the organisms are few, the local defensive process proves destructive to them only; it is where they are present in great numbers and when their virulence is such as to provoke a violent reaction that focal tissue destruction occurs. The areas of tissue thus subjected to autolysis may vary from microscopic spots to large and deep excavated patches which penetrate the external coat and create foci in the media. The initial localized infections also show marked gradations in intensity and serve as foci from which others are formed, either through the distribution of infection in tissues more or less remote, continuity of tissue, or confluence.

The focal areas are at first the seat of an inflammatory process which sooner or later becomes replaced by scar tissue, the sclerosis from which the disease obtains its name. The local inflammation may be acute and brought on by some febrile infection such as typhoid fever, rheumatic fever, tuberculosis, malaria, etc., or it may be of a very gradual development, as occurs where the cause lies in infected tonsils or teeth or syphilis. A striking example of slow development is the form due to syphilis, in which the pathogenic spirochete is of low virulence. Arteriosclerosis due to lues has been given a separate place in the nomenclature of the disease, but unwarrantedly so; its only characteristics are a very gradual development and a predilection for the cerebral vascular system.

In the *aorta* lesions of the intima are areas of various size of a yellowish white color composed in part of fat droplets

rich in cholesterol. These patches may be small and discrete, or involve large areas, in some instances, in fact, the entire lining of the vessel. At first there occurs swelling of the cement substance between the cells, the areas affected becoming the seat of the swellings and patches referred to. As the process advances, the endothelial cells lining the intima break down. The cement substance between the cells dissolves and becomes converted into a hyaline mass with newly formed connective tissue to contain it. The cholesterol freed from its connection with the lecithin (this phospholipoid having been consumed during the autolysis which caused tissue destruction) forms soap with fatty acids, likewise detached from the lecithin and the blood calcium. The soft yellowish magma thus formed, becoming calcified, leads to the formation of the characteristic atheromatous patches.

The middle layer of the artery or media, the unstriated circular muscles of this layer, become necrotic in patches, some small, others more extensive. Relaxation of the affected muscles may cause widening of the lumen of the artery affected instead of the reduced caliber which intimal lesions produce. In the vessels of small caliber, the arterioles in particular, the intima becomes the seat of an inflammatory process with active local lymphocytosis, and peripheral fibrosis which tends to narrow the caliber of the vessel and impair its rôle as a propulsive channel. The process just described applies particularly to the *renal arterioles*. The media may, however, undergo another process, *i.e.*, hypertrophy due, as I have submitted, to excessive activity of the adrenals and the distribution to the intima

through the vasa vasorum of arterial blood excessively rich in all constituents, including lipoids, all of which, acting concomitantly, provoke tissue autolysis and its lesions.

The relation of blood-pressure, arteriosclerosis, and contracted kidney was studied by the writer in 1165 cases, all but 17 being over 40 years old. He concludes from the clinical and pathological material studied that arteriosclerosis alone does not cause hypertension even if the small renal and cardiac vessels are involved, but that renal changes produced by the sclerosis of the smaller vessels lead to arterial hypertension. The appearance of hypertension is independent of the severity and extent of the anatomical lesion. The writer concludes that every patient with persistent hypertension has already a renal lesion. Harpuder (*Deut. Arch. f. klin. Med.*, cxxix, 74, 1919).

In the *coronaries* and their ramifications in the myocardium, the nodular form with its yellow bulges and streaks is the main type observed. Affecting mainly the inner coat or intima of the larger vessels, it tends more or less to narrow their lumina and to cause distortion. Fortunately, the lesions usually progress but slowly to the stage of degeneration and atheroma. They are usually most marked in the left coronary, that which receives the blood richest in autolytic bodies owing to its proximity to their sources, the adrenals, thyroid and pancreas and to the source of oxygen, the lungs, whence they are first distributed through heart, aorta, and coronaries to the heart itself, etc. The lesions, as regards the lipoids, resemble those observed in the larger arteries, the aorta in particular, the coronaries being frequently involved when aortic nodular endarteritis occurs. The myocardial ramifications of the coronaries are fre-



quently included in the morbid process, but compensation is readily established and perpetuated through collateral arterioles.

In some instances the character of the inflammatory reaction is quite unique, with the accumulation of curious fat-containing cells (endothelial), which in their subsequent course liberate the lipoid materials in the atheromatous mass. This type of lesion is very common in individuals of middle age, and when it does occur in one of the small vessels it may lead to a severe impairment of the nutrition of portions of the myocardium. O. Klotz (Annals of Clin. Med., Apr., 1926).

Coronary sclerosis sometimes occurs independently of aortic lesions, but is apt to coincide with similar degenerative processes in the brain. The lesions occur in the intima, are nodular, and are frequently the seat of calcareous deposits. This applies also to the vessels of the basal ganglia which, as I showed in 1907, are closely related to the functions of the pituitary body. Cerebral arteriosclerosis tends to the formation of aneurysmal dilatations and degeneration, and if a high blood-pressure prevails, a suddenly assumed recumbent posture, bending over of the body, or mental excitement, may give rise to cerebral hemorrhage or apoplexy.

The *calcium metabolism* is an important feature of these cases in the light of my views, Waldemar Koch, of Chicago, having long ago found that insoluble calcium is always precipitated when lecithin is withdrawn from the blood and that lecithin rendered the calcium salts soluble when administered internally. During the growth process calcification of the arteries is apt to be less active, owing to the utilization of this element for the development of the osseous system.

During childhood and adolescence the proportion of calcium in the arterial walls is low, due to the drain upon the calcium resources involved in the skeletal development of the individual. After the age of 40 years there is a sudden rise in the calcium content of the aorta, the average amount being trebled within a short time. The amount rises in abrupt steps with each successive decade. At this period the calcium salts become visible in the arterial walls and may be observed microscopically. Some degree of fatty degeneration appears to be a precursor of sclerosis. In the senile form it is mainly the fatty changes in the tunica media which are of importance. Andrewes (Nederl. Tijd. v. Geneesk., Aug. 5, 1922).

*Non-protein nitrogen* and *blood sugar* were found by Mortensen (Jour. Amer. Med. Assoc., Nov. 28, 1925) to be within normal limits even in well established cases, but *uric acid* was rather constantly above normal, and of 300 cases of the disease examined by this author, only 23, or 7.6 per cent., had a uric acid showing of less than 3.5 mg. (Benedict colorimeter), while 92.3 per cent. gave a higher figure.

**HYPERADRENIC ARTERIOSCLEROSIS.**—This, the third form of arteriosclerosis, is due from my viewpoint, as its name implies, to overactivity of the adrenals. The participation of the adrenals in the morbid process was first pointed out by Josué, of Paris, who found that adrenalin injections could cause the disease in animals. This observation has been verified experimentally by many investigators, who found, however, that the form of arteriosclerosis thus produced did not conform specifically to the familiar type. The arterial lesions produced failed to indicate true sclerotic lesions in animals, while cases in which the vascular tension is high often failed

to show signs of arteriosclerosis. In adrenal arteriosclerosis, the arterioles and the heart, being composed of unstriated muscle fibers, as is well known, are specifically sensitive to the action of adrenal extractives. The small arterioles and the cardiac muscles, besides the middle coat of the larger vessels—all rich in unstriated muscle fibers,—are precisely the ones constricted in this adrenal form of the disease, and which undergo hypertrophy when the excess of adrenal production—hyperadrenia—is sufficiently prolonged.

Experimentally, synthetic and levorotatory adrenalin has twice the capacity to induce atheroma possessed by the racemic product secreted by the suprarenals. Since the vasoconstrictor effects of both products are practically identical, the induced atheroma is not directly related to hypertension. Laignel-Lavastine (*Arch. d. mal. du cœur*, etc., Dec., 1923).

It is perhaps this form, due to overactivity of organs which has long been associated with vascular tension, that Allbutt merged in with forms due, as we have seen, to other causes.

There is as yet no evidence to indicate that the ordinary types of arteriosclerosis have a relation to hypertension. We appreciate that Allbutt was insistent upon such a relationship, but it is our belief that he has confused in his analysis a variety of pathological processes, all of which he designated by the name of "arteriosclerosis," but which he never analyzed to determine the exact character of the arterial lesion. O. Klotz (*Annals of Clin. Med.*, Apr., 1926).

The adrenals have also been associated by both physiologists and clinicians with an antagonistic action to fatigue waste products—a function which fits in perfectly with the fundamental function I have attributed to

these organs, *i.e.*, heat production or thermogenesis, this function, in turn, being the dominant factor of antitoxin, which converts waste products, including fatigue wastes, into eliminable end products. Now, it is precisely the form of arteriosclerosis due to excessive labor or exertion, overuse of the muscles, which produces the lesions of the intima attributed to the adrenals. The actual process itself does not differ, however, from that just described, *i.e.*, tissue digestion or autolysis.

**ETIOLOGY.**—We have seen that senility tends to bring on what has been termed "senile" and by others "physiological" arteriosclerosis. But this morbid process may occur not only as a result of old age, but also in early life and even in infancy, and also as a complication of febrile infections, cancer, etc. Such cases are due, from my viewpoint, to the marked hydrolytic activity of the blood incident upon the defensive process, which entails the destruction of pathogenic organisms, toxins, toxic wastes, detritus, etc., which the blood may contain.

In a series of 2000 autopsies, 442 cases, or 22.1 per cent., according to W. H. Smith (*Boston Med. and Surg. Jour.*, May 7, 1908), showed more or less arteriosclerosis. It is three times as common in the male as in the female, and occurred no earlier in the colored race in this series. The average age of the cardiorenal group was nearly 55. The average age of the cerebral group was nearly 60. Fifty per cent. of the cases of cerebral hemorrhage occurred in the fifth and sixth decades, and it was three times as common in the male as in the female. All the cases of aneurism were in males. The average age of death was nearly 45. Death from gangrene and diabetes was incident to the last decades,—the sixth and seventh; the average age nearly 65.

Two types of vascular sclerosis are recognized by the writer: (1) *Intimal*, nodular or atherosclerosis, produced by

infectious toxins or excess products of protein metabolism, and constituting a rather slow process. (2) *Medial or senile*, or the Mönckeberg type of arteriosclerosis, apparently a more acute process (experimentally, at least), and possibly a degenerative one. The latter type is rarely associated with chronic nephritis and hypertension, but in the former type the circulating poison produces widespread capillary contraction, and as the tissues must have blood, the heart has to contract more strongly. This is further enhanced by spasm of the small arterioles supplying the glomeruli. The cause being toxic, there is reactive inflammation and eventually the glomeruli are destroyed, whereupon the renal tubules atrophy and dilate or are shut off by fibrous tissue contraction. Excessive meat-eating seems harmful to both the arteries and kidneys. L. M. Warfield (Ann. of Clin. Med., Jan., 1924).

Arteriosclerosis has been attributed to the wear and tear of life, and its increasing demands. While this factor has been deemed unimportant by some authors, the fact remains that the great mental stress connected with modern activities and responsibilities impose a correspondingly great increase of cerebral metabolism and production of toxic wastes which are as efficient as causal factors of the disease as any other known agency. In the hyperadrenic type, the dominant causes are, as stated, excessive physical exertion, if long continued, or occupations which involve prolonged muscular effort. These provoke arterial degeneration through the action of the great proportion of toxic wastes of metabolism produced. Proof of this is afforded by many familiar facts. Thus, the right arm of such a subject shows more marked arteriosclerosis than the left, but if the subject is left-handed, the left arm will show the

greater lesions. This applies to the legs of persons who are forced to stand for too prolonged periods. Over-taxed tissues show a marked predilection for the disease; they are the seat of excessive metabolic activity and, if the normal limits are passed, of cellular autolysis. Not only may arteriosclerosis be thus limited to extremities, but to a single system of vessels, and that without the presence of the disease in other localities. The radials may thus be the seat of sclerotic changes and the body or internal organs be normal.

Infectious diseases, owing to the activity of the defensive process they entail and the resulting autolysis to which they expose the portions of the vessels, the intima and media, in contact with the blood-stream, are direct factors in about one-quarter of febrile cases, particularly if prolonged. The bacteria aggregate on or in the vascular tissues, and these become special sites for degenerative changes. Typhoid and rheumatic fever, and particularly influenzal pneumonia, are especially active in this connection. Gout has also been incriminated, but the pathogenic factors of this disease are doubtless the true malefactors, acting as toxics capable of evoking the vascular disease. This applies also probably to toxic wastes of intestinal origin.

The causal relationship between chronic infections and chronic nephritis was studied by the writer in 500 cases with autopsies, and he found a gradual increase in the number of cases of marked general arteriosclerosis up to 60 years of age, and but little increase in severe cases after the age of 65, thus showing that age could not be the determining factor. On the whole, it seemed that a complex mixture of toxic material arising

from infected foci might provoke disturbances in the arteries or capillaries, from which disturbances in the blood-pressure would arise. It would seem, then, that the more severely the arteries were affected anatomically, the greater would be the likelihood of functional disturbances in blood-pressure. W. Ophüls (Northwest Med., Nov., 1921).

Undoubtedly the most productive factor of arteriosclerosis is the excessive use of protein foods, or at least foods too rich in proteins. Considerable experimental study of this question has clearly demonstrated this fact. Various investigators have held that the excessive ingestion of cholesterol in the food was the dominant source of evil. This, however, was shown to be incorrect by more recent investigators. No diet was found to contain cholesterol in the proportions added to the food of experimental animals, or to produce an increase of blood cholesterol sufficient to produce arterial lesions. The pathogenic diet proved to be one over-rich in proteins and fats.

The writer frequently found an increase of cholesterol in arteriosclerosis; this, however, showed no relationship whatever to the degree of hypertension. Likewise in nephritis, he found that excess of blood cholesterol may be present without high blood-pressure. Sisto (*Giorn. di clin. med.*, Apr. 10, 1921).

In an experimental study the writers found that large amounts of protein and not cholesterol had caused disease of the aorta and arteriosclerosis in the experimental animals employed. Clarkson and Newburgh (*Arch. of Int. Med.*, May, 1923).

Retention of fats in the blood is the most important factor in experimental arteriosclerosis of rabbits. The blood-pressure increases as a rule. When this feeding was discontinued, fibrous and muscular proliferation occurred in the vessels. Changes of the coronary

arteries and secondary degeneration of the heart were also frequent. M. Versé (*Deut. med. Woch.*, Jan. 9, 1925).

The writers studied the systolic blood-pressures of rabbits fed lanolin for the production of arteriosclerosis, and control rabbits kept under similar dietary conditions. The observations failed to confirm the conclusions of Fahr, Van Leersum, Schmidtman and Schönheimer that feeding rabbits with cholesterol-containing substances over long periods of time causes elevation in blood-pressure. They also consider that increase in blood-pressure is not an essential factor in the deposition of lipoids in the intima. Shepard, Shapiro and Seecof (*Jour. Lab. and Clin. Med.*, July, 1925).

Excessive protein diets fed to experimental animals for prolonged periods, up to two years, caused extensive arteriosclerosis of the aorta and in many instances of the coronary arteries. Nuzum, Seegal, Garland and Osborne (*Arch. of Int. Med.*, June, 1926).

The active cause embodied in the proteins and fats suggests itself when it is recalled that they are rich in lecithin combined with fatty acids, and that this phospholipoid is the thermogenic agent which renders enzymic autolysis possible. It is an excess of lecithin, therefore, which, from my viewpoint, is the active pathogenic factor insofar as diet is concerned.

Poisoning by such agents as lead, barium, alcohol, tea, coffee, tobacco and other stimulants have all been incriminated. But the element of excessive use can only be taken into account in the agents commonly employed.

The pains of abdominal angina are not always the first signs of arteriosclerosis of the abdominal vessels. A feeling of fulness, sudden hyperacidity, and idiosyncrasies may be due to it. Measuring the blood-pressure is important. Intolerance against nicotine

is a frequent cause. Strauch (Münch. med. Woch., Jan. 19, 1923).

**SYMPTOMS.**—The symptomatology of the disease will be presented as described by our late and regretted predecessor in the article on the same subject, Prof. Guthrie McConnell, quoting his text where possible.

It must be borne in mind that the symptoms of arteriosclerosis depend largely upon the organ involved and upon the extent of the involvement. The disease may start as a defect of metabolism before the production of organic changes in the circulatory system, and some authors hold that there is a prodromal and curable stage of arteriosclerosis.

As long urged by Stengel, various nervous symptoms are to be met with, some of which are results of the disease, while others are due to associated organic disorders. Those who suffer with arteriosclerosis are often affected at the same time with structural disease of the kidneys, heart, brain, etc. The error must be avoided of attributing to arteriosclerosis the symptoms which result from purely accidental organic diseases when associated with it, but not essentially due to it. There is great danger of attributing all the obscure conditions of senility and even of the presenile period to arteriosclerosis.

In many instances there may be a widespread involvement without any disturbance of the general health of the individual, who may seem quite vigorous. The arteries will show an increased hardness, but no one organ may be sufficiently implicated to give rise to symptoms referable to it. The patient may be able to carry on his work, both mental and physical, most satisfactorily, but the discovery of his

condition may be most fortunate in that he can guard against a mode of living that would tend to increase his arterial degeneration. Such a case may show an increasing pallor, an anemic appearance due rather more to a loss of coloring matter of the blood than to an actual deficiency in the number of red corpuscles. There is generally a gradual loss of power, both physical and mental, or at times nothing may have been noticed till the patient suddenly breaks down.

At this time the peripheral vessels will be found to have become hardened and somewhat tortuous, the blood-pressure will be in the neighborhood of 200 mm. of mercury, cardiac hypertrophy may be noticeable, and some casts and albumin be present in the urine. There will usually be a history of neurasthenia, the patient being irritable and suffering from insomnia. Although such instances of general involvement are encountered, as a rule quite definite types of the disease can be constructed according to the predominance of certain symptoms indicating involvement of special organs.

Among 420 patients (not including any cases with loss of compensation on the part of the heart) examined by Dunin, 120 gave evidence of normal or diminished pressure. Some of these patients were not aware of their vascular lesion and complained of only a few symptoms referable to it, but in the great majority angina pectoris, arrhythmia of the pulse, dyspnea, and swelling of the feet were present. He divides cases with increased tension in arteriosclerosis into several groups: (a) Those without subjective symptoms, constituting about 30 per cent. The usual complaint was here referable to nervousness, obesity, or renal or biliary calculi. Some of the severest cases (240 to 290 mm. pressure) belong to this category, and the absence of symptoms can only be explained by a healthy condition of the heart, which was

able to overcome increased resistance in the capillaries. Accentuation of the second aortic sound and a systolic aortic murmur were common. (b) In this group the subjective symptoms were slight or very marked, but the kidneys were usually affected. (c) Here angina pectoris was very common. Angina is much more common with low pressure, but no difference between the two forms concerning general course or prognosis could be detected. The lowest figures obtained (65 mm.) were in cases of angina, and during the attack the pressure often fell 30 mm.

The writers have observed in patients in whom the blood-pressure is high that the pupil is larger than the average normal pupil, with a usual minimum of 4.5 mm. in width. While it contracts promptly to light stimulus, it immediately returns to the original size and there remains, without the light stimulus having been changed. The association of this symptom with the high blood-pressure of arteriosclerosis is so nearly constant as to make it at least strongly suggestive. Wiener and Woldner (Jour. Amer. Med. Assoc., July 17, 1915).

Out of 44 cases in which a gross cerebral vascular lesion had existed, 31 exhibited evidence of retinal vascular disease, while in 19 of these the changes were severe. Of 27 that died, a gross vascular cerebral lesion proved to be the cause of death in 12. R. F. Moore (Quarterly Jour. of Med., Oct., 1916, and Jan., 1917).

Numerous lesions in the eye and the optic nerve may be due to arteriosclerosis. Their early recognition is important in early diagnosis of the latter, especially when localized in the kidneys or in the brain, diabetes and syphilis. There is usually a history of slight hemorrhage in the retina at some time in cases of fatal apoplexy. The writer never found the internal carotid or the ophthalmic artery normal at necropsy after 70. Syphilitic arteritis is always accompanied with a lymphatic infiltration of the wall of the vessel at various points, while senile arteriosclerosis is merely a de-

generative process. He has found isolated foci of atrophy in the optic nerve after 70. These foci are strung along the nerve from the chiasm to its entrance into the eye. E. Fuchs (Siglo Médico, May 14, 1921).

These local manifestations can be considered under three headings: (1) Cardiovascular symptoms; (2) nervous, and (3) renal. Sometimes the pulmonary symptoms may be prominent.

*Cardiovascular Symptoms.*—In the first stages, owing to the increased peripheral resistance, a pure hypertrophy of the left ventricle occurs, and of the right ventricle to a less and variable degree. The area of cardiac dullness is increased and the impulse is displaced outward and slightly downward. There may be reduplication of both first and second sounds, and the latter over the aortic cartilage is accentuated and possibly roughened. In a considerable number of cases the insufficiency of the aortic and mitral lesions is due to a process in the leaflets similar to that which is going on in the vessels. The hypertrophied cardiac muscle may undergo various changes due to the interference with its nutrition. This diminution is due to the increase of the resistance to be overcome and the involvement of the nutrient vessels of the heart by the degenerative processes, so that although the heart has more work to perform, the quality and quantity of the blood-supply have suffered. In consequence of this there will appear parenchymatous, fatty, and fibrous changes in the myocardium. As this occurs there will be more or less dilatation of the ventricle. The patient will begin to complain of palpitation, dyspnea, and shortness of breath on exertion. During such attacks the apex beat will usually be forcible and the pulse one of high tension. A mit-

ral murmur appears, the veins are obstructed, the urine becomes scanty and high colored, and dropsy, gradually increasing in extent, appears. This latter condition is probably due to alterations in the vessel walls, to an increased amount of fluid within the vessels, and to the weakening of the cardiac muscle. In consequence of the diminution of the lumen of the coronary arteries or their branches by the sclerotic changes, the amount of blood that gets to the myocardium will be decreased.

Autopsic study of 86 cases of coronary sclerosis enabled the writer to divide such cases into the following 5 groups: (1) Typical angina pectoris, 24 per cent. of the cases. (2) Atypical angina, usually in the upper abdomen, 2 per cent. (3) Progressive myocardial failure without painful attacks, 26 per cent. (4) Myocardial failure together with typical anginal attacks, 3 per cent. (5) Occult coronary sclerosis, without sufficient evidence for a clinical diagnosis, 40 per cent. In the last-named condition, electrocardiography is diagnostically very helpful, most commonly showing inversion or negativity of the ventricular T-wave. Among other findings in the writer's series of cases were: Coronary occlusion, 15 per cent.; diseased thoracic aorta, 99 per cent.; diseased abdominal aorta, 21 per cent.; syphilis, 9 per cent.; valvular changes, 50 per cent.; myocardial degeneration, 100 per cent.; infarction, 8 per cent.; combined arteriosclerosis of the peripheral vessels, 70 per cent.; of the kidneys, 37 per cent.; cerebral arteriosclerosis, 13 out of 15 brains; gall-bladder disease, 26 per cent.; hypertension, 31 per cent., and sudden death, 37 per cent. F. C. Willis (Minn. Med., Sept., 1924).

The dyspnea increases until the patient is constantly struggling to get the slight extra amount of air that seems needed to relieve him. The

signs of dilatation of the heart become more marked; the apex beat becomes diffuse and develops a gallop rhythm, which on auscultation may be heard over the entire heart. Accompanying this there may be a systolic sound. As a rule, not very much can be done, as the entire cardiovascular system is involved. Occasionally, by means of proper treatment the condition may be greatly improved so that the patient can resume his work. An individual may suffer from numerous similar attacks and have intervals of comparative comfort before the condition terminates fatally.

Cardiac inefficiency should be given its full value as a means of early diagnosis and as an indicator for therapeutic initiative. The great usefulness of test doses of digitalis with or without reinforcement by physical rest constitutes the very foundation of timely diagnosis. Greene (Amer. Therap. Soc.; Med. Rec., Sept. 23, 1916).

Associated with the changes of the heart muscle are, as mentioned above, the degenerative processes involving the *coronary arteries*, particularly a sclerosis. This usually occurs about the orifices, although the main branches or the smaller ones may be affected. This condition may occur uncomplicated by valvular lesions, and in young men may be out of all proportion to the changes in the other vessels. As a result of this one of the most important symptoms is that of *angina pectoris*, which would seem to occur particularly in those cases where there is an increased peripheral resistance, and not in mere stenosis of the coronaries without the increase. (See also the article on ANGINA PECTORIS in Vol. I.)

Outline of the diagnostic points in *coronary arterial occlusion*. The writer

reports 13 cases, of which 5 were fatal, with 1 necropsy. His typical picture includes: (1) Severe anginal pain, substernal or upper abdominal. (2) Pinched ashen gray or very pale facies. (3) Acute emphysematous distension of the lungs with râles at the bases. (4) Easily compressed, rapid, thready pulse with almost any arrhythmia. (5) Sudden dropping of systolic blood pressure. (6) Cardiac impulse if palpable is diffuse and feeble; distant heart sounds with tic-tac or gallop. (7) Localized, evanescent, pericardial friction-rub, coming a few hours or a day or so after the onset, missed if posterior. (8) Fever of short duration and mild type with polymorphonuclear leucocytosis. (9) Inversion of the T-wave with arborization block. Gordinier (Amer. Jour. Med. Sci., Aug., 1924).

The same clinical phenomena may be brought about by involvement of the main branches of the coronaries. Where sudden death has taken place thrombosis of one of the branches has probably occurred, and the heart muscle will show a fibrosis or a small anemic infarct with an extensive fatty degeneration. Under ordinary conditions the decreased supply of blood to the heart may be sufficient to enable it to carry on its functions, but if some sudden demand is made upon the myocardium it is unable to meet the situation. There is a temporary local anemia, and the heart muscle, which is particularly susceptible to a decrease in the amount of oxygen, will contract spasmodically, giving rise to extreme pain that accompanies such attacks. The same muscular cramps will arise in other parts of the body where the nutritive vessel is thickened and a sudden excessive demand is made.

Of the other changes resulting from the sclerosis, *aneurism* is one of great

importance. These dilatations may vary greatly in size, from those extensive ones involving the larger vessels to the miliary type such as are found in the vessels of the brain, the symptoms occasioned depending not only on the size, but also on the location. When located in the brain, rupture may take place at any time, giving rise to hemorrhage of varying extent.

Involvement of the *peripheral vessels* may give rise to various local disturbances, according to the degree of the sclerosis. When there is a sclerosis of the arteries the disease advances progressively, and as this takes place there must necessarily be an interference with the nutrition of the body in general and frequently of certain organs in particular. As the muscular and elastic elements diminish there is an increase in the amount of connective tissue, and at the same time there is more or less atrophy of the parenchymatous portions of the tissues.

The *aorta*, often involved in the disease, responds purely mechanically to the intermittent propulsion of the heart beat. The normal aorta behaves like a rubber tube with thick walls, while a sclerous aorta acts more like a tube of thin steel; it does not stretch, but recovers its primary form more readily. This is noticeable when the pulse wave is examined close to the heart, as in the arm. Its sudden and rapid rise indicates sclerosis of the aorta by suppressing the controlling effect of stretchable aortic walls. This excess of active force in the pulse wave is evident before auscultation and radioscopy give conclusive findings. The differential pulse pressure is also increased, the systolic rising while the



diastolic keeps at the normal figure. A third sign is the relative hypertension in the legs. This may be so pronounced as to be evident with the Riva-Rocci cuff. A fourth is that the femoral pulse precedes the radial, while these are synchronous in health and with abnormally high or low pressure from other causes.

A condition of the *muscles* of the extremities, similar to that of the cardiac muscle in angina pectoris, is quite common in old people in whom the vessels have become sclerotic. On account of the interference with nutrition the muscles very frequently undergo spasmodic contractions accompanied by severe pain. If the sclerosis is more marked there may be considerable atrophy of the part accompanied by various forms of degeneration. In advanced cases the blood-supply may be so interfered with as to produce senile gangrene. This form is usually limited to a single limb, or, if it affects more than one extremity, the lesions are successive in order. As a rule, the lower limbs are the more commonly involved. The lesion is generally quite extensive, implicating a whole toe or a part of the foot, and tends to spread to an indefinite degree. In these cases there may be a greatly diminished pulsation or it may even be obliterated.

Under the heading of *nervous disturbances* in arteriosclerosis come many varied symptoms. These may be due in part to the associated lesions of the different organs. The sudden occlusion or obstruction of a larger peripheral artery, either experimentally by pressure applied from without or pathologically by an embolus within, gives rise to quite characteristic symptoms. There is usually a sudden onset of pain, frequently very violent, and a loss of

power in the part supplied by the obstructed vessel. The pain may subside in a short time, to be renewed if secondary emboli occur, but later the extreme pain lessens and becomes a continuous aching. Sometimes sharp pains may radiate from the point of obstruction. As a rule, the accompanying loss of power is only partial, but may become complete, as frequently happens in embolism of the abdominal aorta, causing complete obstruction. In addition to the pain there may be pallor, coldness, tingling or numbness, weakness or complete cessation of the peripheral pulse; occasionally violent cramps.

Cases of muscular cramp may be set down to arteriosclerosis, according to Rohde. In these cases the diagnosis is often, if not invariably, made by the nature of the palliative remedy.

If a collateral circulation does not become established, gangrene is the usual result. In other cases where the arterial obstruction is less marked than in the above, there may develop such symptoms as coldness, numbness, tingling, darting pains, and finally extreme suffering. From a study of the matter it would seem unnecessary that there should be a neuritis present to account for the pains. Thoma lays considerable stress upon the pain in angiosclerosis, which he says is generally put down to rheumatism. As the basis of the pain he has demonstrated the presence of Pacinian corpuscles in the walls of the vessels. Again, there may be cases in people of advancing years with symptoms similar to the above, and who, in addition, suffer with a stiffness or weakness of the extremities, with a sense of coldness, or of heat, or of some form of paresthesia. These symptoms are more common in the legs than in the arms. The severity of these manifestations

may have a direct relation to the degree of arteriosclerosis, and may increase in direct proportion with the advance of the disease. In other cases it may be observed that the symptoms increase and decrease as the condition of the heart suffices or fails to maintain the circulation in the sclerotic vascular system.

The vascular crises of arteriosclerosis are described by the writer. They may occur in the brain, the chest, the abdomen or in the legs, the latter with intermittent claudication. The chest group comprises angina pectoris and acute edema of the lung. Abdominal crises occur after physical exertion or emotional stress, and seem to be independent of the meals. In the cerebral group there may be attacks of sudden unconsciousness for a few minutes, but no convulsions. The pallor is followed by vasodilation and sweating as consciousness returns. In a case described, these attacks return every 3 or 4 weeks. B. L. Duran (*Progresos de la Clinica*, July, 1918).

Mention may also be made of a large group of more or less painful affections of the extremities associated with arterial disease, in which the symptoms suggest the intervention of spinal or reflex vasomotor conditions between the arteriosclerosis and the acute manifestations. Among these are: erythromelalgia, Raynaud's disease, "dead fingers," and intermittent claudication. All of these conditions occur in persons who have more or less decided arterial disease. In the first three the nature of the attacks and paroxysmal character of the vasomotor phenomena suggest that reflex nervous influences play an important part, but the association of marked arteriosclerosis and the constantly recurring circulatory disturbances suggest that the reflexes have their origin in the arterial disease.

So far as *intermittent claudication* is concerned, this peculiar manifestation has been generally accepted as being due to arteriosclerosis. The symptoms do not differ from those already referred to, but the pains, paresthesia, stiffness, cramps, and weakness are distinctly the result of effort. Some hold that these symptoms result directly from the inadequacy of the blood-supply when the muscular effort makes greater demand upon the circulation. Others have thought that vasomotor spasm results from the exertion and causes the symptoms. In proof of the first of these views it has been shown that painful cardiac attacks associated with coronary disease lessen when the myocardium has grown considerably sclerotic, in consequence of which the need of active circulation is less imperative than in the case of a more normal heart muscle.

Case of intermittent claudication in a man, aged 72, with syphilis of over 50 years' standing. Necropsy showed that the lameness, which had started 2 years before, was due to arteritis obliterans affecting the abdominal aorta, both iliac arteries, and particularly the tibial arteries. The inflammatory lesions involved chiefly the middle and outer coats. Infiltration of the arterial walls with cholesterol was less manifest than in diabetes. Letulle, Heitz and Magniel (*Arch. des mal. du cœur*, Aug., 1925).

Various authors maintain that a nervous element plays a part by exciting vasomotor spasm, and in proof of this cite the facts that coldness, pallor, and weakness of the pulses are frequent symptoms of the attacks, and that claudication is especially likely to affect arteriosclerotic people who have a general neurasthenic condition as well. On the other hand, it is significant of the purely obstructive character of the

vascular trouble that claudication has been universally recognized as a forerunner of gangrene. In erythromelalgia—the red, painful neuralgia—arteritis obliterans has been found in many cases.

Largely as a result of the anemia of the brain and the consequent interference with nutrition there are certain *cerebral manifestations* of arteriosclerosis. Many of these conditions are in all probability due to partial thrombosis of larger cerebral vessels or to complete thrombosis of smaller branches. Partial thromboses of the larger vessels are seldom absent in cases of extensive arteriosclerosis of the circle of Willis. These thrombi cause a rather rapid encroachment on the lumen of the vessels, and thus interfere with the circulation in a manner more abrupt and violent than does the narrowing of the lumen from increase of the arterial disease itself. Of the early symptoms, headaches of a distressing character are frequent. As a rule they are associated with an increase in arterial tension and are commonly relieved if the pressure be reduced. Usually frontal and continuous, they occasionally may be paroxysmal, resembling migraine. Another symptom commonly present is vertigo, generally transient, but most distressing. It is often brought on by a change of posture from sitting to standing, emotion, sudden exertion, etc. This deprives the brain of the proper amount of blood and hence causes the symptoms.

Tests of internal ear functioning in the diagnosis of cerebral arteriosclerosis were studied by the writer, who recorded 1026 cases. In most of these the ear disease overshadowed pathologic conditions elsewhere. Vertigo was the usual symptom. Tinnitus proved especially instructive; it oc-

curred at intervals or continuously, but in the course of perhaps many years organic disease of the auditory nerve became manifest. Failure of all treatment of the tinnitus indicated actual organic injury in the domain of the auditory nerve. Stein (Zeit. f. klin. Med., xc. 1-2, 1920).

In a review of 100 cases of cerebrospinal arteriosclerosis the writer found vertigo the commonest symptom, occurring in 46 cases. About one-fourth of the patients were amnesic for recent events. Headache and paresthesia were common. The pupils were small and sluggish in 25, and arcus senilis existed in 16. Deafness was marked in 8 and moderate in 8. Over one-fourth of the cases had apoplectic seizures. Sensory symptoms were insignificant and motor paralysis slight. Attention is called, however, to the frequent occurrence of the symptom-group of ataxic paraplegia. Progressive mental deterioration and emotional instability were common to all the cases. The age at which the symptoms had first been noticed averaged 60.9 years. G. E. Price (N. Y. Med. Jour., Oct. 3, 1923).

Vertigo may be associated with epileptiform seizures owing to the disease of the cerebral arteries. Such patients have attacks of dizziness, headache, twitching of the muscles, and extreme weakness. In some, compression of the carotid arteries will cause the symptoms to appear. The resemblance to petit mal may be quite marked. These attacks may be accompanied by momentary loss of consciousness or bewilderment, followed by slight clonic convulsions affecting the arms and legs, but not beginning in any particular member and ending with a period of mental confusion and aphasia lasting from a few minutes to an hour. There may also occur transitory disturbances of function of parts of the brain or cord, leading to hemiplegia, mono-

plegia, aphasia, or even paraplegia. Recovery from an attack is commonly complete, and the patient is able to go about his daily affairs as usual. Again, the attack may appear in the form of coma and stupor, which can continue for hours or even days, with ultimate recovery. The cause of these doubtless may be an incomplete uremia in some cases, or other form of toxemia, but the sudden relief of symptoms that so often occurs is evidence that they are more usually dependent upon the condition of the cerebral circulation.

One of the commonest symptoms of *cerebral arteriosclerosis* is a gradual failure of the mental powers. An individual no longer shows the same interest in his affairs, becomes careless and apathetic, his memory and judgment are at fault, the facial expression is dull, and, with progression month by month, at last the psychological powers are so reduced that the individual is in a state of dementia. These indications of mental degeneration are, however, not often seen as a result of arteriosclerosis in men under 40 years of age. Mental degeneration is common enough as a presenile change in men at or about 60. Rupture of the cerebral arteries leading to apoplexy and thrombosis in consequence of changes in the intima are common events in arteriosclerosis.

*Psychoses* of various forms may make their appearance. The patient becomes dull, develops an uncertain temper; there may be present delusions, imperfect orientation, weakness of intellect; speech is often slow and slurred. There may also occur tremors, differences in the pupils, and exaggerated reflexes. Delusions of grandeur are occasionally observed in advanced cases.

After a study of the psychoses associated with cerebral arteriosclerosis, the writer concludes that there are 3 periods of development: (1) The *involuntary*, where degeneration is caused by the ordinary wear and tear of life; (2) the *toxic*, in which degeneration is caused by poisons of acute and chronic infections and intoxications; (3) that in which degeneration follows *persistant high blood-pressure*. Nack (Med. Rec., Dec. 11, 1915).

In 3 cases observed by the writer there was a distinct degree of confusion and disorientation, with hallucinations. These features were conspicuously lacking in the patient with normal blood-pressure. There was no excess of non-protein nitrogen, urea, uric acid, creatinin or sugar in the blood of these cases; the urine was not microscopically pathologic. J. Bostock (Med. Jour. of Australia, Mar. 1, 1924).

*Abdominal symptoms* may be quite prominent in the form of epigastric pain and intestinal cramp, associated with high blood-pressure and shock of greater or less degree.

The most characteristic feature, according to Rodhe, is the strict localization of the pain in the epigastrium, appearing in persons of 40 or over. The pain is a sharp, stabbing or burning sensation, lasting generally for only a few minutes. It radiates sometimes to the liver, shoulder, or arms, and ptyalism may be observed, with a cold sweat and semiconsciousness. Between the attacks there is no pain, at least in the milder cases; in others there may be a dull, continuous ache. There are generally no other disturbances from the digestive tract, although sometimes constipation, diarrhea, meteorism, etc., may be observed. Other morbid processes are liable to occur in the digestive organs aside from those due to the arteriosclerosis, of course, and the latter may induce thrombosis,

or even actual ulcer formation. The attacks may follow unusual physical exertion. Buch has reported a case in which the attacks were liable to come on when the patient lay down. Emotions and excesses are also liable to bring on an attack. On the other hand, the kind of food has no influence.

The brevity of the painful attack, the radiation of the pains, and the occasional alternation with angina pectoris confirm the diagnosis. The same causes that elicit angina pectoris are noted in the history of these attacks. Pressure on the epigastrium sometimes induces pain similar to that of the typical attack. The pure arteriosclerotic gastralgia subsides or vanishes altogether under diuretics, digitalis, or strophanthus. The syndrome may simulate ulcer, nervous dyspepsia, or even cholelithiasis, until death in syncope occurs and autopsy reveals the unsuspected sclerosis of the coronary, stomach, or intestinal arteries. Jaworsky has published reports of 4 such cases in which the patients succumbed suddenly.

Though rare, arteriosclerosis of the abdominal vessels may induce symptoms suggesting angina pectoris, gastric trouble or attacks of meteorism. J. A. Hedlung (*Hygiea*, lxxvii, No. 9, 1915).

Abdominal arteriosclerosis with obstruction of some mesenteric artery should be suspected when there is paroxysmal pain in the abdomen, with bloody vomiting and stools, and sometimes ileus. In a case reported by the writer in which the necropsy alone cleared the diagnosis, the first symptom had been sudden agonizing pain near the umbilicus, accompanied by incessant vomiting, both rebellious to all measures. The pain became diffuse but persisted intense. Death ensued in 36 hours as the man was being prepared for a laparotomy. Necropsy re-

vealed obliteration of a group of mesenteric arteries. Martinez (*Revista Españ. de Med. y Cir.*, Feb., 1921).

The vessels of the pancreas may show an extreme involvement, as is frequently the case in regard to the spleen. Sclerotic changes in the uterine vessels may give rise to marked disturbances. Infarcts may occur, or there may be hemorrhages from the endometrium. This latter type usually occurs after the menopause and, as a rule, has to be treated by hysterectomy.

Impotence from arteriosclerosis due to *cavernositis chronica*, sclerosing inflammation of the corpora cavernosa, is not generally recognized. The patient, above middle age, complains of curvature of the penis during erection until coitus becomes impossible. G. F. Lydston (*Med. Fortnightly*, May 11, 1908).

Some loss of functional power of the uterine muscle is the predisposing cause of bleeding in cases of arteriosclerosis. This loss of functional power is due either to the development of fibrous and elastic tissue from subinvolution or to the condition which caused this subinvolution. Chalfant (*Jour. Amer. Med. Assoc.*, Jan. 28, 1911).

*Renal Symptoms.*—As many of the associated symptoms in general arteriosclerosis are due to renal involvement, lesions of this organ will be dealt with separately. This lesion of the kidney is responsible in a large percentage of cases for a considerable elevation in blood-pressure. This elevation is, however, definitely connected with arterial spasm in general, and may involve organs other than the kidneys. There may be found a small, contracted kidney associated with an extreme grade of arteriosclerosis which may be regarded as secondary and due partly to the high pressure and partly to toxemia.

There is no evidence that arteriosclerosis is a precursor of, or an essential

factor in, the production of chronic nephritis, but rather that arteriosclerosis may make its appearance in the renal vessels in 1 of 2 ways; either as an independent arterial disease unassociated with the changes contained within the kidney structure (in which case it involves the main renal arteries), or it makes its appearance in the small arterioles of the renal parenchyma concurrently with lesions appearing in the glomeruli and intertubular stroma. It is not uncommon to find that lesions comparable to those in the renal arterioles are to be found simultaneously in the small vessels in many parts of the body. O. Klotz (Can. Med. Assoc. Jour., Apr., 1925).

The true kidney of arteriosclerosis, however, is a red, beefy organ which is firm, hard, and dark in color, not at first reduced in size, sometimes, indeed, slightly enlarged. Very often with this kidney there may be few or no urinary symptoms. In a late stage there may be found large, flat areas of atrophy of the cortex, or a large section of one organ may be involved in consequence of an obliteration of the arteries passing to the part. The urine in these two groups presents striking differences. In the small, contracted kidney the amount is increased, the specific gravity is very low, the albumin small in amount, often absent in the morning, hyaline casts are present, and very often red blood-cells as well. The urine of the arteriosclerotic kidney may contain at first no albumin, or, if present, the amount is not large; the specific gravity is normal or sometimes high. Later, the albumin may be present in large amount, and sometimes, as when a patient is admitted with an attack of cardiac dilatation, the urine is scanty, usually containing a large amount of albumin and numerous tube casts due to an intercurrent nephritis. In consequence of

the renal changes there may appear many symptoms indicating a special involvement of this organ by the sclerotic process.

The earliest manifestations are usually a hardness of the pulse or a slight edema. Dropsy, however, may be totally absent for a long time or altogether, particularly if the heart be much hypertrophied and little dilated. Occasionally there may be a good deal in the later stages, especially when the hypertrophied heart has become dilated so as to permit of regurgitation through the mitral orifice. This may be accompanied by a definite mitral murmur, though the valve flaps may be perfectly healthy. In such a case there may be pulmonary apoplexy with hemoptysis, and the dropsy may take on many of the characteristics of that of cardiac origin, which, indeed, it partly is. It may become considerable and general and affect not only the legs, but the pleura and peritoneum. Vomiting and various forms of gastric disturbances may be present. Many inflammatory affections may appear; bronchitis is exceedingly common; pneumonia and pleurisy are frequent, as is pericarditis. The brain is also involved, particularly when the kidneys are becoming insufficient to carry on their work, and symptoms of uremic poisoning appear. The patient sometimes becomes restless and irritable; in the advanced stages transient delirium or temporary mental failure with delusions may occur.

Of the symptoms resulting from renal deficiency that of *uremia* is the most alarming, while its cause is unknown. Inasmuch as the character of the uremic manifestations is so strongly suggestive of a toxic origin, investigators have, for the most part, sought to explain them as the results

of the accumulation in the blood of a poison or poisons. The obvious association which exists between uremia and deficient functional activity of the kidneys naturally suggested that the toxic material might be found among the end products of metabolism which it is the function of the kidneys to secrete. No substance, however, among the normal excretory products has been found that will cause the symptoms observed. Consequently many hold the view that the manifestations are due to some intermediate product of metabolism.

The discovery of hemorrhage in the kidneys, eyes, or brain may lead to the diagnosis of arteriosclerosis. The kidneys are an important site of hemorrhage, and careful examination of the urine will often reveal the presence of erythrocytes. G. Evans (Brit. Med. Jour., July 5, 1924).

One of the later symptoms of uremia is uremic asthma. In such cases the patient, whose breathing at ordinary times is normal or nearly so, may be suddenly seized in the early part of the night with agonizing dyspnea. The attack is like one of bronchial asthma with cardiac additions. There is an extreme want of breath with violent inspiratory effort and urgent orthopnea. There is much palpitation and cardiac distress and apprehension. After an attack lasting perhaps a couple of hours, the difficulty yields with wheezing, coarse crepitation and the expectoration of frothy fluid. This is sometimes blood tinged or accompanied with separate sputa containing bloody mucus. The dyspnea and distress subside, the respiration resumes its former tranquillity, and nothing remains of the paroxysm except the prostration. As a rule, the attacks will not be so severe, but will be manifest to a less degree.

Of the nervous symptoms due to uremia, headache, often of a neuralgic type, may be the first to appear. Various other disturbances may occur toward the end: changes in manner and temper, dullness, drowsiness, sometimes sleeplessness, and occasionally great restlessness. Speech may be slightly affected and the patient show transient mental failure.

*Disorders of vision* are quite frequent. In some cases they are due to albuminuric retinitis and to optic neuritis, but in many instances complete amaurosis develops in association with uremic symptoms. In such cases there may be no changes in the fundus of the eye that can be detected with the ophthalmoscope. The sudden onset and transient character of the amaurosis also are hardly compatible with the presence of an organic lesion. Actual blindness may be preceded by a period of dimness of vision, or the stage of dimness may be at no time overstepped. Sometimes the patient may emerge from a convulsive attack completely amaurotic, or the blindness may be, for a time at least, an isolated symptom of uremia. The loss of vision may persist for a few hours or less, or for a few days. The pupils usually retain their activity.

The eye is the organ where arteriosclerosis is often manifested earliest, and where it can most accurately be appreciated by study of the background. Retinitis, especially the degenerative form of albuminuric retinitis, rather than the inflammatory variety, indicates arteriosclerosis. The latter is apparently not mentioned among the etiological factors of choroiditis, but it is reasonable to assume that it might be responsible for this, as well as for retinitis. In arteriosclerosis, hemorrhages into the vitreous humor follow rupture of ves-

sels of the retina and choroid. Arteriosclerosis may also prove active in the pathogenesis of glaucoma. Elsworth Smith (Interstate Med. Jour., Jan., 1914).

Examination under a 16-magnification of the small arteries and arterioles of the fundus oculi is highly important. While all patients with hypertension do not show vascular changes, cases with arteriosclerosis show marked changes, to wit: Increased tortuosity of the retinal vessels, with alterations in size and breadth, broadening of the light streak, and occasionally a beaded appearance; dipping or cupping of veins as they cross the retinal arteries—due to the arterial thickening—with occasional dilatation of the veins peripherally to these points; edema of the retina with hemorrhages, usually linear or flame shaped, and occasionally, small exudations; blurring of the optic nerve head, usually beginning in the superior nasal quadrant, and at times marked optic neuritis; pigment disturbance about the macula, described as a "moth-eaten appearance" and caused by changes in the vascular supply; arteriosclerosis of the choroidal vessels, a rarely seen but significant condition. C. A. Clapp (Arch. of Diag., Apr., 1919).

The *pulmonary symptoms*, other than the uremic asthma, are bronchitis and emphysema, with failure of the right heart. Cases have been reported in which the pulmonary artery has shown very extensive atheroma and sclerosis, with but little involvement of the systemic circulation. Special localization is common in this area.

Primary sclerosis of the pulmonary arteries is indicated by the combination of a diastolic pulmonary murmur with enlargement and insufficiency of the right heart, cyanosis, and clear heart sounds. X-ray examination should be carried out. The patients in this disorder are relatively young. Mobitz (Deut. Arch. f. klin. Med., Mar. 30, 1923).

**DIAGNOSIS.**—A careful consideration of the foregoing discussion will indicate that although there are many symptoms referable to the arteriosclerosis, nevertheless there are many variations from the typical picture. As has been shown, there may be a very extensive portion without equal changes elsewhere. The peripheral vessels may show marked changes without the aorta exhibiting similar conditions, and *vice versa*. Little can be determined from the general appearance of the patient. He may appear robust and never have complained of sickness, yet his vessels may show extensive disease. Nor can much reliance be placed upon the presence of the *arcus senilis*, as it may be found in middle-aged men with good arteries.

A perceptible pulsation in the supraclavicular fossa, with the wave traceable to the axilla, points to sclerosis and dilatation of the *thoracic aorta*. Other evidences include an abnormal dulness over the vessel and at the right of the sternum, and an exaggerated, metallic second aortic sound. C. Trunccek (Rif. med., June 18, 1923).

The following cardinal manifestations in a case of arteriosclerosis are usually well marked: (1) Thickening of the peripheral vessels; (2) signs of hypertrophy of the left ventricle, shown by the apex beat dislocated outward, the thudding first sound, and the accentuated aortic second; (3) heightened blood-pressure; (4) a slight and variable amount of albumin in the urine. As a rule, these symptoms are present in a large proportion of the patients when they first come under observation. Superficial vessels, as a result of the sclerotic changes, may be visibly dilated and tortuous, as in the temples. The brachial arteries may show similar conditions, but if not visible can be recog-



nized by palpation. Care should be taken not to mistake a simple increase in the tension for a thickening of the vessel walls, although the two are commonly associated. In making an examination the vessel should be firmly compressed so as to obliterate the pulse and then felt below the point of pressure. Sometimes it may be well to empty a small section of the vessel and palpation made between the two points of pressure.

In a study of 100 cases the writers noticed a clear contrast between cases with advanced arteriosclerosis of the peripheral vessels (radials, brachials and temporals), but normal retinal vessels and blood-pressure, and cases with sclerosis of the retinal vessels and high blood-pressure. Evidently the peripheral vessels play little or no part in producing hypertension. It is sclerosis of the smaller vessels, such as the retinal arteries (which serve as an index of small vessel sclerosis), that cause high pressure. Ophthalmoscopic examination thus assumes great value. Retinal changes co-existing with low blood-pressure suggest an earlier hypertension which has disappeared or lessened through heart weakness. O'Hare and Walker (*Arch. of Int. Med.*, Mar., 1924).

The left ventricle will, as a rule, show signs of hypertrophy, but it may not always be demonstrable to percussion on account of being covered, more or less, by an emphysematous lung. This latter condition is also quite common in the aged, in whom sclerosis is frequently encountered. The pulse is prolonged, hard, and tense, with a very characteristic sphygmogram—one having a slow, oblique ascent, a broad top, a slow descent, and an absence of the dicrotic rise, which in the normal state depends upon the elasticity that is absent in the diseased vessel.

Bulging in the subclavian arteries, where they turn to a right angle to the axis of the aorta, when the walls of the latter have lost their elasticity, is a sign of sclerosis of the aorta. As the aorta cannot stretch, the blood entering it at each pulse wave races with its usual violence into the artery beyond and hits against the upper wall of the subclavian artery at this point. The bulging where it hits this wall can be easily felt with the finger with each pulse wave. Trunczek (*Münch. med. Woch.*, Feb. 10, 1914).

Although the X-ray picture does not show the incipient stage of arteriosclerosis in the peripheral vessels, it is very helpful for the demonstration of later stages. In very similar cases it is negative, because the process in the arteries has not yet resulted in the deposition of calcium salts, or because the periodic ischemia is due to spastic conditions of the small arteries. L. Nielsen (*Münch. med. Woch.*, July 10, 1925).

Of considerable aid in the diagnosis is the blood-pressure; the majority of cases will show a distinct rise. In some instances early in the disease, or before the thickening of the vessels is evident, the blood-pressure may be persistently high. A pressure of over 160 milligrams of mercury can, as a rule, be considered the boundary line between the normal and the abnormal. Up to about 200 mm. one can generally come quite close to a correct estimation of the pressure, but above that point an instrument of precision becomes necessary. In many cases of even well-marked arteriosclerosis the blood-pressure is not raised. This may be because the disease is localized to a part of the arterial tree, or because the heart may at last be giving up the struggle, and hence the pressure, once high, may have fallen.

Capillaroscopy appears to be a diagnostic help in the detection of early

arteriosclerosis. If, upon giving nitroglycerin, no resulting capillary dilatation is seen, a definite indication of the disease exists. A negative test, however, does not exclude a progressive arteriosclerosis. A. Crespo (*Arch. de card. y hem.*, June, 1924).

Localized sclerosis of the splanchnic vessels gives rise more easily to increased arterial pressure than the same amount of disease elsewhere. The increase may also be due to a localized anemic condition of the brain, it having been shown in such instances that the blood-pressure has risen tremendously, evidently an endeavor upon the part of the body to force blood into the anemic area. It must be remembered, however, that in a given case of sclerosis in which the blood-pressure is found to be raised it cannot be assumed that the pressure is high because of the disease of the arterial walls, nor yet that the sclerosis is due to the increased pressure. The arterial stiffening may be, for instance, the result of syphilis, and the high blood-pressure, of some intercurrent condition of a nervous or toxic nature which may be more or less removable by appropriate treatment.

Arterial thickening in children is familial and non-syphilitic in origin, and is found in very young children who are born with a thickening of the whole of the arterial system. It occurs in most of the children in the same family. It can readily be detected, the artery being felt to roll under the finger, by exerting very gentle pressure with the finger tips. A thin child deficient in growth suggests the possibility of arterial thickening. Vipond (*Brit. Jour. Childr. Dis.*, Jan.-Mar., 1926).

**TREATMENT.**—We have seen that the dominant pathogenic rôle is played by proteins, and that these owe their morbid effects, in the light of my researches, to their lecithin con-

tent. Such being the case, the aim should be, not a quantitative reduction of foods as is now generally recommended, but a **protein-low diet**, reducing particularly those which are known to be rich in lecithin. Thus, eggs, the yolk in particular, which serves for the preparation of pharmaceutical lecithin, fish roe, calf's brain, sweetbread, fats, bone-marrow, meats (especially pork, beef and mutton), cream and cheese, oily fishes such as salmon and shad, all contain a relatively large proportion of lecithin. We might, therefore, better characterize the indication as a **lecithin-low diet**. Conversely, the proportion of this phospholipoid is low in most of the other foods, particularly in vegetables and fruit and somewhat less so in fish and fowl, while game, deer and rabbit, for instance, approach closely the proportion of red meats. In general, however, all proteins contain lecithin as physiological thermogen, and it is only the relative proportion of it which should be taken into account.

Attention should be directed to the lessening of the toxemia, which is generally recognized to be due to nitrogenous bodies. In the intestinal tract certain bodies of the aromatic series are produced by the decomposition of protein materials, and these, being absorbed, may, either by direct action on the vessels or in some less direct way, produce vasoconstriction. These poisons must first pass through the liver, and, if this organ be active, may be destroyed there and do no harm. It seems to be especially the protein of meat and eggs that produces most toxins. If the toxins once reach the blood they are chiefly got rid of by the kidneys. Rudolph (*Brit. Med. Jour.*, Nov. 26, 1910).

It is often said that the treatment of arteriosclerosis is preventive, but this should be taken to include the

prevention of extension of the morbid process. If the latter is not sufficiently advanced to cause mechanical interference with the circulation or with the adequate blood supply of important organs, a virtual cure may thus be reached even though the atheromatous or sclerotic areas remain. Indeed, these are intended to preserve the functional integrity of the vessel as a blood channel, the elastic and muscular elements of normal vessels serving to aid the *vis a tergo* motion of the blood stream.

An important factor in this connection is that high viscosity of the blood tends to increase its autolytic activity especially upon the endothelium of the intima and the muscularis of the media. The free use of **water** as a beverage—though avoiding excess—will tend to eliminate this source of danger while counteracting also the cause of high vascular tension.

As a preventive of oncoming arteriosclerosis in those predisposed, the writer orders a **protein-low diet**, prohibits stimulants, prescribes **open-air life**, **breathing exercises** and **calisthenics**, and gives **sodium citrate**, 30 Gm. (1 ounce) daily by mouth in 2 or 3 doses between meals in not over 100 c.c. (3½ ounces) of an aqueous menstruum. In established arteriosclerosis of mild or intermediate severity, the daily amount of citrate is increased to 50 to 100 Gm. (1½ to 3½ ounces), and **potassium iodide**, 15 to 30 drops of a saturated watery solution, added. In severe cases the iodide is omitted but the citrate given regularly in full dosage. The diet is **lactovegetarian**. R. Paolucci (Morgagni, Jan. 6, 1924).

**Baths** of various sorts have been recommended, but as the end usually desired is a **free sweating**, the particular method by which that result is obtained is not of great importance.

The immediate effect of the above is to produce a drop of from 10 to 20 points in the systolic pressure. This reduction is, as a rule, quite transient, but it will be found that the general symptoms seem much improved by the treatment.

The **warm, full bath** dilates the capillaries and lowers the blood-pressure; five minutes is a sufficient time. Cold bathing is injurious; swimming is not allowed because the cold water contracts the superficial capillaries, which when combined with the violent exercise may raise the blood-pressure dangerously high. C. W. Watson (Jour.-Lancet, Mar. 15, 1914).

In the **carbonic acid brine baths** the salts in solution exert more action than the gas bubbles. These baths are best given at 32° to 34° C. and the cold bath is reserved for cases with subnormal intravascular pressure with a flaccid arterial wall. Slowing of the pulse is constant and important, and is due to a lengthened diastole, thus resting the heart muscle. J. H. Honan (Med. Rec., Feb. 5, 1916).

The rôle of **heat** in warm baths emulates Nature's own way of counteracting the effects of poisons. It acts as does the formerly feared fever. The toxics, as they pass through the cutaneous vessels, are subjected to increased hydrolysis by the tissue enzymes, whose digestive activity is increased precisely as it is in the body at large by the action of adrenoxidase on lecithin, which augments the liberation of heat energy. Sajous (Med. Jour. and Rec., Sept. 15, 1926).

The value of **iodide of potassium** would seem to be negated by the modern interpretation of the pathogenesis of the disease, in which the thyroid hormone stands as activator of the proteolytic process by increasing the thermogenic efficiency of the tissue lecithin. But, as we have seen, the lesions thus produced are due to the increase of defensive activity of

the blood, which is exerted more actively upon toxic wastes, toxins, bacteria, etc., than it is upon the tissues. Such being the case, a sudden spurt of defensive activity caused by the iodides will result in a widespread destruction by the blood and its phagocytes of the pathogenic agents whatever they be, and these will cease to act as antigens, *i.e.*, to stimulate the continuous production of enzymes, etc., which insidiously cause the arterial lesions. The dose generally recommended is 10 grains (0.65 Gm.), freely diluted, three times a day, in an adult.

Iodides have a marked hypotensive action in high blood-pressure without arteriosclerosis. In advanced arteriosclerosis with high blood-pressure iodides have no hypotensive action. To produce a beneficial effect in hypertension, 10 grains (0.65 Gm.) of **potassium iodide** should be the initial dose. This should be rapidly increased if necessary. Organic iodides—in the therapeutic doses recommended—contain too little iodine to be efficient. Only in cases in which iodides are contraindicated by alimentary disorders should **sajodin** be substituted in corresponding doses. Matthews (Edinburgh Med. Jour., Mar., 1911).

The iodides are contraindicated where the hemolytic action of the excess of antibodies secreted has produced a secondary anemia and, so to say, thinned the blood. Martinet has published cases in which they were actually harmful. These were characterized by high blood-pressure, but evidently due to the arteriosclerosis and its effects: the narrowing of the arterial lumen in various arterial segments. He, therefore, rightly deems potassium iodide contraindicated when the hypertension is accompanied by abnormally low viscosity of the blood;

when the heart or kidneys have little or no reserve force; when the kidneys are unquestionably insufficient, and, above all, when a hemorrhagic tendency is manifest. Such patients are constantly menaced by uremia and cerebral hemorrhage. Aside from these conditions, however, he considers **potassium iodide** capable of rendering valuable service.

Various drugs have been used to lower the blood-pressure. As to the propriety of using such drugs there is much discussion, many holding that the high blood-pressure is a compensatory process; that it is an attempt to maintain an adequate speed of capillary flow through the kidney or other organ which would otherwise be impossible. There is, however, no certain correspondence between the amount of urine secreted and the degree of blood-pressure. If a **nitrite** is given to lower blood-pressure there frequently will be an increase in the amount of urine.

Clinicians in increasing numbers object to the use of drugs which influence the blood-pressure, on the ground that the tissues have become accustomed to the new standard, and that it would be unwise to interfere. That this view is correct in some cases is shown by the fact that some patients are much more disturbed and uncomfortable with the pressure lower than it was before.

Of the drugs most generally used **nitroglycerin** is often effective, but, according to Osler, it is rarely given in large enough doses, and even then is liable to be very transient in its effects. It is best given in solutions freshly made, in doses of 1 to 3, 4, or 5 minims (0.06, 0.18, 0.24, or 0.3 c.c.) of the 1 per cent. solution three or

four times a day. In crises of high tension larger doses may be given. It does not seem to do any harm, but as individuals react so differently to the drug it is well always to test it upon each patient. It tends, as in my own case, to produce severe headache.

The **nitrites** are useful when the high pressure is not wholly due to anatomical changes, but also to a certain spastic condition of the vessel walls. At times the **spirit of nitrous ether** in  $\frac{1}{2}$  dram (2 c.c.) doses, repeated, suffices to afford relief, but for continued use **sodium nitrite** is the best. Its action is more prolonged and is not followed by the unpleasant cerebral disturbances that frequently result from the use of nitroglycerin. In doses of 1 to 4 grains (0.065 to 0.26 Gm.) every three to four hours it may be of great service. Small amounts should be given and be gradually increased until the desired effect is obtained.

In cases with persistent hypertension the writer uses a modified Lauder Brunton draught:—

℞ *Sodii nitritis* .... gr. xlv (3 Gm.).  
*Sodii carbonatis* (C. P.),  
*Potassii nitratis*,  
 āā ..... ʒj (32 Gm.).  
*Aqua* ..... q.s. ad fʒiv (128 c.c.).

M. Sig.: Shake well. One teaspoonful in a goblet of hot water before breakfast.

In rebellious cases, usually associated with sclerosis, the remedy is given before each meal. In many cases of uncomplicated hypertension small doses of **chloral** (0.3 Gm., or  $4\frac{1}{2}$  grains) will, with attention to the digestive system and thorough emptying of the intestinal tract by means of **salines** and the use of **alkalies**, cause a decided drop of blood-pressure and relief of symptoms. Pounding, irritable hearts with hypertension, with or without vertigo and

discomfort referable to the head, are, as a rule, relieved by the administration during two or three weeks, three times daily, of from 1 to 1.5 Gm. ( $15\frac{1}{2}$  to 23 grains) of **strontium bromide** with from 2 to 4 drops of tincture of **veratrum viride** or of **aconite**. H. L. Elsner (Amer. Jour. Med. Sci., Jan., 1911).

In disturbances of digestion and arteriosclerosis **theobromine** acts as a specific remedy against abdominal pains; in such cases, from 2 to 3 Gm. (30 to 45 grains) are to be given daily. Tincture of **strophanthus**, in doses of 4 to 8 drops, given twice or three times daily, has also had good results. A. Pick (Med. Klinik, May 12, 1912).

The warning against the use of **chloral hydrate** in cardiovascular disorders given in numerous text-books is unwarranted and has done harm in preventing the employment for hypotensor purposes of a drug both more efficacious and less injurious than the nitrites. Chloral is, with **bromides**, one of the best relievers of general and circulatory spasm. The sleep induced by chloral hydrate is characteristically followed on awakening by an abundant diuresis, as much as a liter of urine being passed in 6 or 8 hours, with manifest euphoria, relaxation from nervous tension, and lessened difficulty of breathing. A small dose of chloral suffices in some instances to overcome the inhibiting angiospasm and produce diuresis. **Chloral** and **caffeine** make sometimes the combination of choice for diuretic purposes. A. Martinet (Presse méd., June 5, 1916).

When there are indications of an inadequate ventricle, as shown by the existence of edema, gallop rhythm, or the occurrence of attacks of acute dyspnea, it may be necessary to use **cardiac tonics**. **Digitalis** is not necessarily contraindicated by the high pressure, as it is seldom that this drug increases the tension sufficiently to endanger the vessel wall. Not infrequently the pressure will fall after its

administration, probably because the drug brings about a better oxygenation of the blood by bracing up the pulmonary circulation.

Where complications of various kinds are present, notably anginal pains, or true angina pectoris, I have used with marked success **theobromine or theobromine sodio-salicylate**, 5 grains (0.33 Gm.) 3 times a day, reduced to 1 dose daily when the symptoms for which it is administered are alleviated. They possess the great advantage of promoting a gentle dilatation of the arterioles while giving rise to no untoward effects if administered in the dose mentioned. Excessive dosage produces tinnitus aurium and other cinchona-like effects. The persistent and continuous use of theobromine, 5 grains (0.33 Gm.) once daily, after disappearance of the acute symptoms will prevent their return.

**Diuretin, or theobromine sodio-salicylate**, is the most effective and most used drug, employed in doses of 10 to 15 grains (0.65 to 1 Gm.) three times a day. So prompt and satisfactory is its action in cases of this kind that its use has been recommended as a means of diagnosis in doubtful cases. Its effect depends on its powerful action in overcoming the vessel spasm and dilating the arterioles so that they allow a greater flow of blood to the sclerosed areas. Akin (Jour. Amer. Med. Assoc., June 5, 1909).

Various symptoms among those enumerated early in this article require individual attention as they arise. Lydston asserted that **thiosinamine**,  $\frac{1}{2}$  grain (0.013 Gm.) 3 times daily gradually increased to 1-grain (0.06 Gm.) doses, actively antagonized the morbid process.

Partial relief from headache and dyspnea is frequently afforded by **thiosinamine**. Daily doses of 0.06

to 0.10 Gm. (1 to  $1\frac{1}{2}$  grains), by injection or ingestion, produce no untoward effects. The blood-pressure descends only after prolonged administration. Rénon (Bull. de l'Acad. de méd., Apr. 25, 1911).

**Theobromine sodio-salicylate (diuretin)** is very effective in relieving the sweet taste of arteriosclerosis. On suspension of the drug in a personal case, the disturbance returned, but it was again cured in the same way, and the patient now takes this drug continuously and has been free from the trouble for a year. Similar benefit was realized in another case in which the patient complained of attacks of pain in the tongue of arteriosclerotic origin. A. Müller (Zentralbl. f. innere Med., July 15, 1911).

In addition to the more specific methods of treatment as given above, there are various general factors to be considered: Naturally the removal, as far as possible, of the underlying causes. All **focal infections** should be **eliminated** or at least counteracted by remedial measures, surgical or pharmaceutical.

The causal treatment includes the **removal of foci of infection**, *e.g.*, in the teeth, tonsils, sinuses, ears, gall-bladder, appendix or genitourinary tract; the **prevention of chronic intoxications**, as by alcohol, tobacco, lead, intestinal stasis, and proper **treatment of acute or chronic infectious diseases**. The diet should comprise  $\frac{2}{3}$  to 1 Gm. of protein per kilo. of body weight (in adults), with enough fats and carbohydrates in addition to meet caloric needs. The food should be distributed evenly in the 3 meals. **Exercise, relaxation, recreation** and 8 or 9 hours of **sleep** are of great importance, and hurry and worry must be avoided.

In the palliative treatment, **warm baths, woolen clothing and moderate exercise** are advised to relax the skin vessels and peripheral arteries. For those who cannot exercise enough, **massage** is a good substitute. **Hydrotherapy** is helpful, but the extremes of

heat and cold should be avoided, especially in hypertension. **Iodides** help improve the cerebral and asthmatic symptoms. Head fulness or vertigo is often relieved by **hydrotherapy**, attention to the alimentary tract and **alkali diuretics**. For nocturnal polyuria, fluids should be reduced to a minimum after 3 or 4 p.m. and all irritants such as condiments and meat extractives be excluded from the diet. Paresthesias are best met by **counter-irritants** and **massage** in the direction of the venous return. F. B. Utley (Atlantic Med. Jour., Mar., 1924).

An extended holiday or a let-up in work—not a complete cessation, however, unless there are signs of cardiac failure or marked mental symptoms—should be recommended. The patient should be told that there may be many years of fairly active life in store for him if he will ease up his existence and live moderately in all things.

For the wealthy, a course at **Royat, Aix-les-Bains, Carlsbad, or Marienbad** sometimes proves very efficient, especially if the dietetic measures and graduated exercise in the open air which form part of the treatment are carefully carried out. The therapeutic value of various mineral springs has been ascribed by some to radioactive properties of the waters; proof of this, however, is not as yet adequate.

C. E. DE M. SAJOUS,  
Philadelphia.

**ARTHRITIS.**—Many forms of joint inflammation have been described, and in practice it is sometimes extremely difficult to distinguish one from the other. Under the present heading will be considered only the form of chronic joint disease variously termed *Arthritis Deformans*, *Hypertrophic Arthritis*, *Osteoarthritis*, *Rheumatoid Arthritis* or *Rheumatic*

*Gout*, from which may be distinguished the condition known as *Atrophic Arthritis*, which differs from the hypertrophic form in both pathogenesis and treatment.

The other forms of joint inflammation will be considered under **JOINTS**, in Volume VI, and under **RHEUMATISM**, in Volume VIII (see Index).

### ARTHRITIS DEFORMANS.

**DEFINITION.**—A chronic disease in which the dominant trend is a progressive localized autolysis of the synovial membranes, cartilages and bony tissues of the joints, with the formation in and around them of osseous proliferative masses and adhesions which deform them and inhibit more or less their functions (Author's definition).

**SYMPTOMS.**—A distinguishing feature of arthritis deformans is its tendency to involve but a few joints, at least at first. Beginning, for instance, with a single finger joint on one hand, it may then extend to the corresponding joint on the other hand; then, after a period of apparent improvement, recurrence and extension to other joints occur, with aggravation of all symptoms.

Often the first joint affected is that of the hip, which swells very gradually as a rule, and becomes increasingly painful, particularly on movement. There is, however, but slight if any redness. On comparative palpation of the two hips, with the hands over the trochanters, a difference will be detected between them; the affected side will be found doughy and fuller, with some increase of tissue tension. This is due to the presence of an exudate which, in cases due to infection, may involve the

whole joint. Then other joints, one or more, may become affected, those of the extremities, then those of the trunk, the vertebræ, etc., until, in some severe cases, every joint finally becomes the seat of the morbid process.

When the hands, which also are often first affected, are the seat of the deforming process, there is a tendency of the fingers to be deflected externally, *i.e.*, towards the radius, and to overlap one another, the thumb remaining free. The phalanges are also the seat of swellings owing to the presence about them of osteophytes in addition to the periarticular swellings due to infiltration.

The finger joints are frequently the seat of another form of swelling known as *Heberden's nodes*, particularly in women in their fourth decade. These cause swelling and pain especially when compressed, and are sometimes congested. They may improve for a while, then undergo exacerbations, with new periods of remission, but each access seems to augment their size and the discomfort they cause, finally leading to the formation of hard projections on the phalanges which usually result in marked distortion of the fingers. Heberden's nodes seem to limit themselves to the fingers.

In some instances the hands are less affected than other regions. The muscles of the areas or extremities involved also undergo an inflammatory process, followed by contractions. The muscles of the lower extremities may thus cause the thigh to become flexed upon the abdomen, and those of the foreleg upon the thigh. The upper extremities sometimes react similarly to the disease, the patient becoming virtually helpless.

The heart muscle taking part in the morbid process, cardiac complications are sometimes observed. The nervous supply of the areas involved being itself the seat of morbid changes, paresthesiæ and evidences of impaired nutrition of the skin and nails may appear. The vertebræ are often affected, causing a well established form of arthritis known as **spondylitis deformans**. The gastrointestinal canal may also be disturbed, due mainly to involvement of the gastrointestinal musculature in the general myositis. Owing in a measure to the pathogenic poisons or toxins, but in great part to his sufferings and growing invalidity, the patient may become extremely irritable, morose and even melancholic.

The progress of the disease is subject to many variations. It may last a long or short time, then cease more or less abruptly owing probably to arrest, automatic or remedial, of the pathogenic agency, the patient finally regaining his normal health. Or, this ending may occur after implication of a few joints, leaving him more or less invalid if the lesions have been at all severe.

A febrile state with exacerbations may coexist, with more or less abnormal perspiration, rapid pulse, anorexia, recurrent indigestion, and some degree of secondary anemia. Many of the cases which proceed to general invalidism, however, do so without showing marked symptoms.

A form of arthritis deformans identified as **Still's disease** differs from the above form in that it is observed only in the young and that enlargement of the lymphatic glands, including those about the joint, is often present. It begins as a rule before



the second dentition, and occurs in girls with greater frequency than in boys.

The onset of Still's disease is usually insidious, one or more joints becoming stiff and thickened. Occasionally the disease develops suddenly with more or less fever. Tachycardia and exophthalmos have been observed. The joints first involved are usually the knees, wrists and cervical vertebræ, then the fingers and finally the toes, several joints being involved simultaneously. No grating of the bone surface can, as a rule, be detected; nor is there a tendency to osseous ankylosis or suppuration. Muscular atrophy is also observed in Still's disease, but with a marked tendency to contracture. The spleen is usually enlarged, its size corresponding in a measure with the severity of the joint lesions.

The course of the disease is generally slow, and its tendency is to cease its devastating effects when the patient has been converted into a cripple, unless pulmonary and cardiac complications, which are apt to occur in a mild form, assume lethal proportions.

**ETIOLOGY.**—In the light of modern knowledge, chronic arthritis is always due to some form of toxemia. This may be due to infection originating from practically any organ, the so-called focal infections. As pointed out by Frank Billings, the commonest foci are the tonsil, the lymphoid tissues of the pharynx, pyorrhea alveolaris, gingivitis, and the sinuses of the head. Then come bronchiectatic cavities, chronic ulcers of the gastrointestinal tract, chronic appendicitis and cholecystitis, and infections of the urinary and genital tract in both sexes. Finally, local submucous

or subcutaneous infections may appear anywhere in the body.

The writers collected data on the *end results* in 411 patients. Of these, 309 (75.2 per cent.) answered a questionnaire sent them several years after treatment; 71 had recovered, and 142 had improved. A similar questionnaire was sent out 4 years later, and replies were received from 226 (54.9 per cent.). The investigation confirmed the view that arthritis is an infectious disease, and that it is usually caused by strains of streptococci, which are usually non-hemolytic and of low virulence, and occasionally by non-pyogenic strains of gonococci, or even by other mild bacteria. The bacteria reach the joints through the blood stream, and lodge in the small vessels of the periarticular tissues, the terminal vessels of the subserosa, and in the branches of the nutrient artery which end in the epiphysis. The effect of a bacteriemia on the host is dependent upon the virulence and number of bacteria in the blood stream. The resistance of the host may be further diminished by exhaustion and debility due to overwork, starvation, chronic diseases, and other factors. Billings, Coleman and Hibbs (Jour. Amer. Med. Assoc., Apr. 15, 1922).

Various types of streptococci, the *S. viridans* and *S. hemolyticus* in particular, isolated either from the tonsils, infected teeth or other regions, have been found, when injected into animals, to cause arthritis of the deforming type. The gonococcus is the main pathogenic organism in the genitourinary tract.

Study of the etiology of arthritis at the U. S. Base Hospital, Camp Lewis. In 89 per cent. of the cases some infectious process other than that in the joints themselves was found and treated. The blood cultures were all negative. The types of infection were the *S. hemolyticus*, *S. non-hemolyticus* and *S. viridans*. The hundreds of cases examined simultaneously showed about the same proportion of streptococci.

The particular germ present in a tooth or tonsil is not necessarily the sole causative factor in the joint condition. The absence of gastrointestinal disease was noted. Not a chronic gall-bladder case nor appendiceal infection was found in the entire series. About 25 per cent. of the cases came in wrongly diagnosed as gonorrheal rheumatism. Medical men are too prone to diagnose gonorrheal arthritis. Harding (Calif. State Jour. of Med., Jan., 1921).

The rôle of infections was investigated in 2973 cases of deforming arthritis. These were divided into 2 groups; in one the infection was in the mouth, nose and throat, or upper zone, and in the other, in the intestine and its appendages, or the lower zone. The opsonic index was used as a criterion of the patient's resisting powers to streptococcus. Strains isolated from various infections brought out marked differences in opsonic index. It became plain that there was a selective influence at work and that affinities seemed to exist between strains of bacteria isolated from the same location in different persons. It was noted that an arthritic patient usually exhibited a low resisting power to one particular strain of streptococcus. Most cases seen had infections in the lower intestinal zone, for the most part in the cecocolon; these patients were observed to have very often a low resistance to the streptococci isolated from the cecocolon. G. A. Persson (N. Y. Med. Jour., Sept. 19, 1923).

Case in which polyarthritis appeared first in the mother, then in the child. The presence of a similar *Streptococcus viridans* in the mother's blood and baby's joint fluid, and the absence of local signs, indicating a portal of entry after contact or other infection, pointed to an intrauterine infection of the infant through the placenta by the organisms circulating in the mother's blood. Richdorf and Griffith (Amer. Jour. Dis. of Childr., Feb., 1926).

The World War afforded ample opportunity for the study of chronic

arthritis, Ralph Pemberton (Trans. Phila. Co. Med. Soc., Apr. 16, 1921) having placed the number of cases at 40,000. This aggregate tended to show that most types were probably referable to the same pathology, and that perhaps the great majority were referable to the same underlying cause. In 400 cases among soldiers, Pemberton found that exposure played an important rôle in inducing attacks, aside from that of focal infections, to which he adds dysentery. The knee was the joint most frequently involved, as in civil life; drilling produced no greater incidence of the disease in that joint. The ankle and shoulder followed.

The basal metabolism was found, in the 20 arthritics studied, to be below normal in 20 per cent. There seemed to be no serious disturbance of the nitrogenous elements. Withholding red meats, for example, seemed to have no specific support. As to blood calcium, no disturbance could be detected at the fasting level, although the contrary sometimes occurred as the bones became rarefied.

A definite relation between blood creatin and carbohydrate metabolism was noted. In 50 per cent. there were high blood creatin values; some fell to normal as the case progressed. There was no  $\text{CO}_2$  disturbance, as shown by the absence of acidosis. The output of water and salt was studied; it suggested a little lag in the output of water and salt as compared to the normal, indicating that the kidney function was somewhat involved. But this played no rôle in the production of the disease. The incidence of arthritis was greatest when metabolism was low physiologically. An undue food intake un-

doubtedly produced arthritis, however, in those in whom the ground-work was laid.

Arthritis deformans occurs about equally in both sexes and at any age except early infancy, unless we include Still's disease. The white race is far more vulnerable to it than the colored—in the ratio of 20 to 1, if we exclude gonorrheal and tuberculous arthritis, reviewed elsewhere (see Index). Exposure to cold and wet are exciting factors in predisposed subjects.

Traumatism seems to predispose the injured area, especially the spine and larger joints, to chronic arthritis. Some families show a predilection to the disease, the view being thus favored that in some instances arthritis deformans may be inherited. The onset of the disease is favored by poor hygienic conditions, deficiency of sunlight, excessive physical labor, etc., all of which conditions lower the defensive powers of the body at large, and thus favor the development of foci of infection. General diseases of an infectious type, influenza in particular, actually foster the formation of such foci in almost any region, and thus become indirect causes of arthritis deformans.

Relation of chronic arthritis to industrial accident cases discussed. A man at work falls, or twists, wrenches or strains either his spine or a large joint. Immediately, or after an interval, he complains of pain and disability. X-ray films show the spurring and lipping characteristic of the form of arthritis known as hypertrophic arthritis, osteoarthritis or arthritis deformans. In the past the opinion has been strongly held that the bone changes were the direct result of the trauma, but recently this view has been challenged, for a number of reasons. Bone can

be injured in only one way—by fracture; it cannot be strained, sprained or suffer contusion. The gross bony changes in these cases must have been present before the injury. The disease of the joints occurs almost invariably after middle life. Alveolar abscesses and intestinal parasites are found in most of these cases. The writer has not seen a single case unconnected with accident work in which a simple trauma resulted in permanent disability. Areas of aseptic necrosis in the immediate vicinity of the joints constitute the fundamental pathology of the disease. L. W. Ely (Cal. and West. Med., June, 1924).

Still's disease, according to an increasing number of authors, is probably but a form of secondary infectious arthritis deformans in children. It does not seem to show sufficiently distinct characteristics to warrant placing it in a separate class.

In a case of Still's disease the little patient had evidence of systemic infection from numerous foci in her mouth about her teeth. From these a staphylococcus and a streptococcus were isolated, and when injected into rabbits caused joint lesions from some of which the typical streptococci were recovered. Extraction of the infected teeth, cleaning up the oral infection, and the administration of an autogenous vaccine produced a marked amelioration in the severity of the patient's disease and completely checked the recurrent periods of febrile reaction. A. S. Rosenfeld (Jour. Amer. Med. Assoc., July 14, 1917).

**PATHOGENESIS AND PATHOLOGY.**—With the endocrine organs as I have defined their functions as factors of the morbid process, we are dealing with an anabolic destruction concentrated in and limited to the joint structures. The pathogenic bacteria, their toxins, toxic wastes, etc., provoke therein an active defensive reaction in which,



Arthritis Deformans.

Erosions in the cartilage and bone with peripheral outgrowths



besides the bacteria and other pathogenic agents, the tissues themselves are subjected to hydrolysis and gradually eroded. As I have previously shown, this process is carried on by the tissue proteolytic enzyme trypsin, the digestive activity of which is enhanced by the local liberation of an excess of heat energy through the interaction of the adrenoxidase and lecithin.

The *creatin*, *creatinin* and *non-protein nitrogen* of the blood and urine of 40 cases of arthritis and 9 normal controls were ascertained. About one-half of the cases of arthritis showed an abnormally high value for blood creatin. Some patients showed a decline in blood creatin concomitantly with clinical improvement. Only 3 of the cases showed creatinuria, while 2 showed an abnormal elevation of non-protein nitrogen of the blood. The investigation suggests that a considerable amount of creatin is included in the precipitation of the proteins of whole blood and plasma. Pemberton and Buckman (Arch. of Int. Med., Apr., 1920).

In clinical calorimetry tests the writers found in all cases of severe type, of long duration and showing great deformities, a *basal metabolism* close to the average normal rate. The *respiratory quotients* were normal and there was no evidence of abnormal respiratory metabolism after large test meals of glucose and protein to indicate an inability to oxidize either protein or carbohydrate. *Nitrogen equilibrium* was maintained, except when the nitrogen intake was cut to a very low level, and there was no evidence of a toxic destruction of protein in chronic arthritis. The observations did not indicate that arthritis deformans was a disease of metabolism, and if infectious in origin, it was not accompanied by increase in metabolism or toxic destruction of body protein. Cecil, Barr, Du Bois, Soderstrom and Magill (Arch. of Int. Med., May, 1922).

The first tissues attacked are probably the capillaries, the proteolytic destruction giving rise to the local effusion, often hemorrhagic, observed, which also affects in severe cases the synovial membrane. Hence the very marked congestion of the latter noted when the joint is opened, and the roughened or corrugated appearance of its surface. As we have seen in the case of the intima of the arteries in arteriosclerosis, the damaged areas then become fibrous, if not destroyed, or are converted into tubercle-like masses. Here also we may find calcareous deposits. Often, as the synovial membrane is undergoing the destructive process, the underlying cartilage is involved, becoming the seat of erosions of varying size, sufficient in some instances to bare the underlying bone. The lesions are well shown in the annexed colored plate.

In the bone proper the lesions are hypertrophic in the sense that outgrowths are formed at the edges which include at times the neighboring tissues, articular cartilage, ligaments, fibrous elements, etc. They may be of various sizes, from the nodes (Heberden's) on the phalangeal joints which so deform the fingers to the large femoral, tibial or spinal masses which annul or block the functions of the joint. The lesions bespeak the nature of the process I have pointed out, an autolytic or autodigestive process carried on by the defensive enzyme, rendered unduly active by an excessive development of heat energy.

Hypertrophic arthritis is chronic from the start, and but rarely exhibits acute periods. The pathology involves the bone, not in an atrophic way, but in a proliferative way. While new

bone is produced, instead of being absorbed, absorption does take place in cartilage where weight-bearing occurs, *e.g.*, the hip, knee and ankle; the bone itself increases. J. L. Porter (Ill. Med. Jour., June, 1926).

**TREATMENT.**—The first requisite in this connection is **removal of the foci of infection**, the most frequently observed of which are located in or about the teeth, the tonsils, and the sinuses. None of the regions liable to become centers of infection, and which have been enumerated under **ETIOLOGY**, should be neglected.

Chronic endocervicitis as a focal infection promoting chronic arthritis emphasized. The streptococci of the cervix are, in particular, concerned and have an affinity for joint tissues. Möench (Jour. of Lab. and Clin. Med., Feb., 1924).

Removal of the focus of infection is often sufficient. The commonest is the dental. Except in root-filled or extensively filled teeth, the X-ray is reliable. Cases due to thickening of the periodontal membrane have, however, been seen. In the second stage of the disease, with definite arthritic changes, the systemic bacterial toxins must, in addition, be neutralized. Billington and Crabbe (Brit. Med. Jour., June 21, 1924).

The cecum and colon are not infrequently the source of intoxication where the more common factors are absent, or may coexist with any one of them. **Free saline purgation**, by causing flushing of the whole intestinal canal, or **lavage of the colon** in milder cases, proves useful in this connection.

In all of the writer's cases the most common source of infection was the colon. In the order of their frequency, the organisms found were *B. aerogenes capsulatus*, single Gram-positive cocci and diplococci, *B. putrificus*, pathogenic types of *B. coli communis*, staphylococci, and streptococci. The etiological

factor is probably a focal infection in the intestinal canal. Having found that colon infection often is responsible for polyarthritis, the writer orders a **diet high in calories**, but **low in calcium**, and strains of viable *bacillus coli* administered **by rectum**, with considerable success. Bassler (Amer. Jour. Med. Sci., Sept., 1920).

Since having recourse to **colonic irrigations**, together with systemic treatment, recoveries have been far more frequent than under the older system. Twinch (Med. Jour. and Rec., Apr. 15, 1926).

Simultaneous stimulation of the defensive functions is the next indication. **Autogenous vaccines** (*S. viridans*) have been recommended by some, but the multiplicity of causal organisms renders this procedure dubious, and the result likewise. Efforts have been made to evoke a sufficiently active reaction by employing vaccines of various kinds of non-specific organisms. The colon and typhoid bacilli and Coley's toxin, the latter prepared from cultures of a virulent streptococcus with *B. prodigiosus*, long used in the treatment of sarcoma, are prominent examples in this direction.

The writers used **colon bacillus vaccine** intravenously, the initial dose being as large as possible—50 to 200 millions—and the patient staying in the hospital 1 day. A rise of temperature to 100° to 103° F. (37.5° to 39.5° C.) in a few hours, often with chill and vomiting, follows, with improvement, as a rule, in 2 days. Perkins and White (Brit. Med. Jour., Mar. 10, 1923).

In 426 administrations of the same vaccine the writers had cyanosis and dyspnea in but 1 instance. Of 11 sub-acute cases 8 cleared up entirely, while 15 cases improved as regards the main symptoms: pain, stiffness and range of motion. Laurie (Med. Jour. of Austral., Mar., 1923).

**Coley's toxin** was administered intramuscularly, the writers having concluded that while intravenous injections did not permit the dosage to be accurately gauged, the intramuscular method overcame this defect—an important feature when a small dose could produce a violent reaction. Starting with but  $\frac{1}{4}$  of a minim, they doubled the dose until a reaction occurred, first at 5 days' then at 10 days' intervals. A given reaction could usually be duplicated with an increase of from 50 to 75 per cent. Increased soreness in the joint may follow the first 2 or 3 injections. A period of amelioration follows, however, increasing in length with each injection. These results were obtained during the inflammatory phase of the arthritis, the injections being supplemented with other measures. Torrey and Klein (Amer. Jour. Med. Sci., Feb., 1924).

The general defensive functions of the body may also, from my viewpoint, be enhanced by stimulating the endocrine glands, notably the thyroid, parathyroid and adrenals, which take an active part in them. In 1907 I recommended **mercury biniodide** in small doses ( $\frac{1}{16}$  grain—4 mgm.) for this purpose, or a course of the **iodides** if the heart be diseased; if not, **thyroid gland** in 1 grain (0.065 Gm.) doses after meals. Since then a relationship between the endocrine organs has been emphasized by many authors—to such a degree, in fact, that an "endocrine arthritis" has been added to our already overencumbered nomenclature of joint disorders, while a connection between arthritis and exophthalmic goiter, and also with acromegaly, has been advocated by others. In truth, hyperthyroidism should normally be present in all toxemias to promote thermogenesis and the antitoxic process. The administration of **thyroid gland** or of

the **iodides**, therefore, augments the efficiency of the defensive functions. Care should be taken, however, not to administer more than the dose I have used for over 25 years, *viz.*, 1 grain (0.065 Gm.) three times daily.

Treatment based on removal of focal infection is not complete merely with the removal of the infecting focus. The body chemistry is disturbed. The agents which combat slowed metabolism include: **arsenic**; probably **potassium iodide**; certainly **thyroid extract**, when it can be used. Ralph Pemberton (Med. Rec., Apr. 16, 1921)

Cases of the hypertrophic type present evidence of endocrine hypofunction, seemingly of the thyroid, with low metabolic rate, slow pulse, low blood-pressure and generally lowered tone. The writer recommends 3 grains (0.2 Gm.) of **thyroid** a day. H. K. Thompson (Boston Med. and Surg. Jour., Apr. 2, 1925).

In recent years, I have used in addition **parathyroid** in  $\frac{1}{10}$  grain (0.006 Gm.) doses, not only to activate the thyroid with which it is given, but also calcium metabolism, which is defective in arthritis.

Attention has been directed by a few observers to *allergy* as the cause of some cases of arthritis in which no clearly defined focal area can be detected or where foci of infection have actually been found and eliminated without affording relief. **Skin tests**, if possible, followed by the **elimination of pathogenic foods**, have given good results.

Case of a woman aged 30 who had had rheumatism in various joints for 2 years. By skin tests she was found sensitive to corn, pork, cheese, flounder and tea. Upon elimination of these from the diet improvement began at once, and after 6 months she had no more pain. In a woman of 57 who had had arthritis of the fingers, hand



and wrist for 7 years, and reacted to corn, pork, lamb, asparagus, lettuce, coffee and raspberry, removal of these articles from the diet gave relief from pain within 3 months. Turnbull (Boston Med. and Surg. Jour., Sept. 4, 1924).

An important feature of the treatment is **immobilization of the inflamed joints** and **absolute rest** in bed. Most authors advocate the application of **dry heat**, others **moist heat** by means of compresses wrung out of hot water and kept warm by means of a **hot water bottle** or an **electric pad** or flannel bandage. The **electric light bake** is efficient if not too prolonged. By raising the temperature of the affected joints, heat causes a local artificial fever which promotes the bactericidal activity of the arthrodial fluids and phagocytes, and this inhibits the local inflammation. Bier's hyperemia (*q.v.*, Vol. V), recommended by many clinicians as efficient, favors a similar process, but it can be used only when any acute and painful inflammation that may be present has been allayed. **Antiphlogistine** kept around the joint is often very helpful. **Cold**, *e.g.*, **ice-bag**, by lowering the local temperature, is sometimes more efficient than heat.

The **electric light bake** results in loss of CO<sub>2</sub> through the lungs, urine and sweat, and this produces increased alkalinity of the blood and sweat. The baking should not be pushed to the point of causing an intense alkalosis. Pemberton (Ann. of Clin. Med., Sept., 1924).

If there is any deformity, J. L. Porter and other orthopedic surgeons recommend that the joint be very **gently straightened out with traction**. If the hip is involved, the leg is fixed on an **inclined plane** and traction is made in the long axis of the

leg, the inclined plane being then slowly lowered as the symptoms subside. The traction should be sufficient to secure relaxation of the muscles, in order to obviate the stiffness which follows efforts to keep the joint immobile. When the joint is in the best possible position for future use, it is **immobilized**, preferably with **plaster of paris** or **splints**, the former being the better because the patient is less likely to disturb it. The patient is then allowed **crutches**, avoiding, however, the placing of any weight on the joint until it is well, which can only occur when motion in it is sufficiently restricted.

Pain may be prevented by administering **cinchophen** (Warfield), or **acetylsalicylic acid** in 10-grain (0.65 Gm.) doses.

While in some cases it is impossible to restore the parts to their original condition, **surgical measures** may be resorted to, particularly in mono-articular forms, to enable the patient to perambulate with some degree of comfort. This phase of the subject is considered under **JOINTS**, to which the reader is referred.

## **ATROPHIC ARTHRITIS.**

**DEFINITION.**—A form of chronic arthritis observed in debilitated subjects, due to toxic waste products of metabolism which evoke a defensive reaction and, incidentally, cause more or less deforming and invalidating lesions in the tissues in which they mainly accumulate—the joints and muscles (Author's definition).

**SYMPTOMS.**—This form of arthritis may be encountered at any age—in adults, adolescents and even children. It is most often observed in the debilitated: Young women, for

instance, in whom, as a result of deficient or defective nourishment, excessive lactation, overwork, or parturition, the endocrines, severely taxed and inadequately supplied with the pabula for the elaboration of their normal secretions, fail to recover their normal activity. The menopause is another period of predilection to atrophic arthritis, owing mainly to deficiency of the ovarian internal secretions, that of the interstitial cells in particular.

Many cases of so-called arthritis deformans of the hip-joint are merely overlooked congenital lesions. Thorough X-ray examination is desirable. Calot (*Bull. de l'Acad. de méd.*, Feb. 19, 1924).

Senile deforming arthritis of the hip-joint frequently escapes detection, the pain being often most marked in the knee or sciatic distribution. To detect the hip involvement, the writer has the patient who complains of pain in the leg cross the latter over the opposite thigh; the hip pain becomes manifest if hip disturbance exists. Before the age of 40, traumatism or exposure are likely to be causal factors, whereas after 40 the age accounts for the condition. Jansen (*Ugeskr. f. Laeger*, July 17, 1924).

In atrophic arthritis the joint lesions may be multiple, affecting usually many joints, large and small, as the joints of the fingers or toes at first, for example, then the elbows or shoulders, knees, hips or spine. It usually sets in more or less suddenly, with pain, redness and swelling, the latter due to an effusion into the joint, and some fever, though the latter is not high as a rule. Periods of exacerbation usually occur, each followed by comparative comfort.

After a series of these symptomatic fluctuations in one joint or another or many simultaneously, signs of

atrophy begin to appear in the affected articulations, each gradually becoming more disabled as time progresses. The joint becomes less mobile as the acute phenomena disappear. The muscles, the skin, hair, teeth and even the nails may show signs of atrophy, the latter, for instance, becoming distorted and thickened. The skin of the feet and hands may be the seat of persistent herpes, blisters, etc., all denoting deficient nutrition.

This atrophic form, in the average case, attacks especially the fingers, causing spindle-shaped swellings which appear as if they were enlargements of the bone, but are in reality the result of a localized effusion. When this effusion is absorbed the part is smaller than normal. The fingers may be shortened and entire phalanges destroyed by the atrophic process.

The X-ray examination affords clear indication of the atrophy, which, beginning in the smaller joints and particularly the phalangeal articulations, progresses until absorption of the cartilage and approximation of the bones has occurred.

#### ETIOLOGY AND PATHOLOGY.

—Atrophic arthritis differs as to its underlying cause from the hypertrophic form in that, instead of being due to toxemias of exogenous origin, such as those produced by toxins, pathogenic organisms, etc., from focal infections—no bacteria being found in the joints—it is produced by toxic wastes, mostly intermediate products of metabolism. As we have seen, the individuals affected, females in particular, are all victims of some factor which lowers the activity of their metabolic processes and general nutrition.

Mainly the joints and the muscles are

susceptible to these toxic waste products. Exposure to cold and damp evokes similar symptoms by reducing the heat energy liberated in the parts exposed, the feet in most instances, and correspondingly diminishing the antitoxic activity (hydrolytic) of the cellular enzymes, thus permitting the accumulation of pathogenic wastes in the blood. The basal metabolic rate is practically always very low in these cases. Marked acidity of the urine, perspiration and saliva also attests to lowered metabolic activity.

In atrophic arthritis the joint fluids become foci for the defensive process, owing to their affinity, anatomical, physiological and biochemical, for wastes.

The fibrous tissues and cartilages first become infiltrated and softened and adhesions form between the synovial membrane and the cartilage. Finally, the ends of the bones become absorbed. Deformities and luxations are frequent. The ends of the bones seem to fuse together, leading to a more or less complete ankylosis of the joint or joints.

A feature which facilitates bone atrophy is the tenderness, so to say, of the subjects—young adolescents, children, females, weaklings, etc.—who constitute the great majority of cases of atrophic arthritis, while the conditions and diseases which predispose to it are all of a debilitating nature. In recent years I have observed this form of arthritis in young women who “dieted” in order to become thin especially about the hips.

In 3 cases of chronic polyarthritis observed, there was no evidence of infection (including tuberculosis and syphilis), but the pharmacologic tests of the sympathetic system gave abnormal results, thus indicating an en-

docrine origin. De Capite (*Pediatrics*, Mar. 15, 1925).

The atrophic type is not due so much to infection as it is to a disturbance of the chemistry and the metabolism of the body. Very likely it is due to dysfunction of some of the endocrine glands. We are coming to think so because the atrophy is so general, while in a few cases we have found that the exhibition of endocrine gland substances is helpful. J. L. Porter (*Ill. Med. Jour.*, June, 1926).

**TREATMENT.**—It has long been observed that such cases are benefited by organotherapy (as I had urged in 1907), but the manner in which the endocrines and the bone changes are related has remained obscure. This can only be explained by the functions I have attributed to the various endocrines, the adrenals, thyroid, and parathyroids in particular. Briefly, all these organs being the dominant factors in thermogenesis or heat-production, and being as such regulators of the defensive activities of the body, atrophic arthritis finds its normal therapeusis in the judicious use of endocrine products and of the agents which influence these organs.

Beginning with the glandular preparations, two of these which are of considerable value to facilitate the autolysis of toxic wastes are **thyroid** and **parathyroid**. An essential feature, however, is the use of small doses only, since large doses, by increasing catabolism, augment the production of wastes and likewise the trouble. Beginning with  $\frac{1}{2}$  grain (0.03 Gm.) of desiccated thyroid and  $\frac{1}{40}$  grain (0.006 Gm.) of parathyroid, the former may be increased to 1 grain (0.065 Gm.) after 1 week. It is of advantage, however, simultaneously to increase tissue oxidation.

This may be accomplished by giving in the same capsule **suprarenal gland**, 2 grains (0.13 Gm.), and **iron carbonate**, 1 grain (0.065 Gm.), to enhance the catalytic activity of the suprarenal product. The capsule containing these agents should be taken after each of the three meals.

In cases due to the menopause, a tablet of desiccated **ovary** (not corpus luteum) of 5 grains (0.3 Gm.) should be substituted for the suprarenal gland, and given separately.

The diet in this class of cases should be as copious as the patient will digest without the least discomfort. To assist physiological assimilation the stomach should be given adequate rest between meals, which means that nothing should be ingested during the intervals except water, which promotes renal elimination. It should not, however, be used in excessive quantities. This is mentioned because if the patients are told that water drinking is helpful they will half drown themselves with it.

Meats should not be restricted, but their use should be so adjusted as to leave room for a fair proportion of vegetables, fruit and fruit juices, the latter to provide alkaline salts, the concentration of which in the blood is very low.

I do not advocate sweating in these cases; it tends further to increase the adynamia, and the lactic acid theory has been exploded by various researches.

A comprehensive study afforded no support to the idea that arthritis, at least of the types studied, is caused or characterized by abnormal production or disposal of lactic acid. This acid has been found to be present in sweat in considerable quantities, making up

about 50 per cent. of the organic acids of sweat. Its presence in this secretion may be referable to the chemical changes occurring in the sweat glands during their activity. The benefit accruing to arthritic patients from sweating measures cannot, in the light of these results, be ascribed to the elimination of lactic acid in the sweat. Cajori, Crouter and Pemberton (Arch. of Int. Med., Oct., 1924).

The use of any form of **artificial light**, preferably the **electric light** or **baking**, is beneficial. By supplying heat energy it increases the antitoxic activity of the tissue fluids and lymphatics, and the conversion of the toxic wastes into eliminable products. **Heliotherapy** is very efficient when available. Any form of artificial heat, however, **diathermy**, even **warm water compresses** or the **hot-water bag**, is helpful by favoring nature's own way of overcoming a toxic process, *i.e.*, raising the hydrolytic efficiency of the tissue enzymes.

At first **rest**, and **weights** sufficient to insure extension of the flexor muscles, but without causing discomfort to the patient, may be needed, but as soon as practicable **passive motion** should be employed. Unlike hypertrophic arthritis, the atrophic type is harmed by any prolonged immobilization. As soon as possible, therefore, the joint or muscles should be given the benefit of **motion exercises** and **massage**, assisted by **electricity** in mild doses. These measures should be resorted to methodically morning and evening, the purpose being to restore motion of the joints and normal and equilibrated contractility of both the flexor and extensor muscles. Persisted in, with appropriate medical treatment, these measures insure good results.

C. E. DE M. SAJOUS,  
Philadelphia.

**ASAFETIDA** is a gum procured by incising the living root of *Ferula fatida*, a perennial herb of the natural order Umbelliferae, native of Persia and Afghanistan. The exuded gum is dark yellow or reddish in color, occurs in regular masses or tears, is very soluble in alcohol, and forms a milky emulsion on trituration with water. Its odor resembles that of garlic and is penetrating and persistent. The principal constituent of the drug, and that to which its odor is due, is a volatile oil, consisting in part of hexenyl sulphide, hexenyl disulphide, pinene, and cadinene (Kraemer); it also contains about 60 per cent. of a resin; a gum; ferulaic, malic, acetic, formic, and valerianic acids.

#### PREPARATIONS AND DOSES.—

*Emulsum asafetida* (emulsion of asafetida, milk of asafetida), containing 4 per cent. of the drug. Dose,  $\frac{1}{2}$  to 1 ounce (15 to 30 c.c.).

*Pilula asafetida* (pills of asafetida), each pill containing 3 grains (0.2 Gm.) of asafetida. Dose, 2 to 4 pills.

*Tinctura asafetida* (tincture of asafetida), containing 20 per cent. of asafetida. Dose,  $\frac{1}{4}$  to 1 dram (2 to 4 c.c.).

Suppositories of asafetida, unofficial, containing the equivalent of 40 drops (2.6 Gm.) of the tincture.

Plaster of asafetida, unofficial, useful as an antispasmodic and mild counterirritant.

**PHYSIOLOGICAL ACTION.**—Asafetida is a stimulant to the brain and nervous system, a powerful antispasmodic, a gastric stimulant and carminative (imparting a sense of warmth to the stomach), a laxative, diuretic, diaphoretic, emmenagogue, and aphrodisiac. It is also a stimulating expectorant. Large doses cause vomiting and purging, nervous phenomena, and burning urination. The drug, or its volatile oil, is eliminated by the urine, sweat, and breath.

**THERAPEUTIC USES.**—The drug is serviceable in flatulence, especially in old people and children. In **infantile convulsions** it is highly useful, given by rectal injection. In the **tympanites of typhoid fever** asafetida is an effective remedy, given by enema. In **hysteria and nervous exhaustion with indigestion and flatulence**, as a stomachic tonic in **dyspepsia** with **flatulent colic**, and as an expectorant in

**chronic bronchitis**, it is also of great value. In **whooping-cough** it acts both as an expectorant and antispasmodic. W.

#### ASCARIS LUMBRICOIDES.

See PARASITES, DISEASES DUE TO.

**ASCITES.**—While this term means dropsy of the abdominal cavity, it is but a division of the general subject of edema, which, therefore, will first be considered.

#### EDEMA.

**DEFINITION.**—The term edema, signifying swelling, is applied to a number of conditions, sometimes in a merely explanatory sense, while in other instances it has reference to a particular feature of a disease, or, with a modifying word, denotes the disease itself. Solid edema, for example, is applied to myxedema, or to swellings which contain a thick lymphoid material. Malignant edema is described as a specific disease. In its common acceptance, however, the term refers to an abnormal amount of serous fluid in the areolar tissues of the body, and results when the transudation from the vessels exceeds the absorption by the lymphatics. The term dropsy is applied to edema of the serous cavities. Anasarca is a universal edema of the subcutaneous and intermuscular spaces. Edema and dropsy are synonymous terms.

**ETIOLOGY AND PATHOGENESIS.**—Although the underlying conditions that give rise to edema are, in a great measure, undetermined, recent investigations and experiments have made material additions to our knowledge of the subject. The factors concerned with lymph formation are to a certain extent operative in the production of edema. A few preliminary statements, therefore, regarding lymph will be appropriate.

Lymph is a fluid which escapes from the blood-vessels, fills the intercellular spaces, and is absorbed by the lymphatics and blood-vessels. The quantity present in the tissues depends upon the amount escaping from the blood-vessels and the amount absorbed by the lymphatics. Different views are held with regard to the processes by which this escape is effected. Stengel holds that the outflow takes place through a more or less permeable capillary wall as a consequence of direct filtration, osmosis, and probable secretion. Hektoen states that lymph formation is the result of diffusion, filtration, and if Heidenhain be correct, an active secretory function of the capillary endothelial cells. Bainbridge, reviewing the recent experimental work of others and referring to his own, believes that nothing is known concerning the physiological variations in the permeability of the capillary walls, regarded under normal conditions as constant, but that this is not so in disease. The theory that lymph formation depends upon intracapillary pressure and capillary permeability holds its ground, but there is a tendency to attach more importance to vital changes in the capillary endothelium.

The gross edema in the head and neck regions of rabbits and cats produced by the administration of paraphenylendiamine is due to increased capillary permeability, independently of the sensory and motor nerve mechanisms, axon reflexes, etc., and of a number of other factors. This edema can be prevented by continuous injections of low concentrations of epinephrin and by drugs (strychnine, santonin, picrotoxin and nicotine) which increase the output of epinephrin from the suprarenals. P. J. Hanzlik (Cal. and West. Med., Jan., 1926).

Basing their views, in a measure, upon the theories held with regard to the cause of lymph production, recent writers consider that filtration from pathological variations in blood-pressure, transudation from increased permeability of the capillary walls, and osmotic and other processes depending upon changes in tissue activity are the main sources of edema. Additional supposed factors are changes in the composition of the blood, decrease of elasticity and pressure in the tissues, obstruction to the flow in the lymphatics, the action of bacteria and toxins, and chemical changes. All of the last mentioned are more or less connected with the others in the relation of cause and effect, and it is necessary to consider them in detail.

Filtration through the arteries or capillaries as the result of active hyperemia is rare, and would occur only when the veins are obstructed; but it is difficult to escape the conviction that the dropsy of passive hyperemia is not partly due to mechanical filtration from direct pressure within the vessels. The fact that in cardiac disease a certain amount of intracapillary pressure is probable, and that the edema appears first in the most dependent portions of the body, is an argument of some weight in favor of the view expressed.

The increase of permeability in the capillary walls is advocated by many as one of the most important causes of edema, and as a probable factor in all edemas. Indeed, this condition, rather than filtration, is stated to be the result of long-continued passive hyperemia, the pressure of which is supposed to set up nutritive disturbances and diminished elasticity of the extravascular tissues. Hydremic ple-

thora, so called, although it occurs in the early stages of cardiac dropsy, is not sufficient, when experimentally produced, to cause edema. Bolton's experiment, in which he produced cardiac edema by tying off portions of the pericardial sac and compressing the heart, demonstrated that neither the venous nor the arterial pressure was materially affected. The veins apparently accommodate themselves to the increase of blood. The deduction is that passive hyperemia causes increased permeability with transudation rather than filtration from mechanical pressure, and that the effect is brought about by deficient oxygenation, and imperfect nutrition of the capillary walls. In the same manner local edema may follow local passive congestion.

Another cause of increased permeability is a change in the composition of the blood, which acts indirectly and is brought about by the action of toxins and bacteria, which, in addition to their influence upon the blood itself, stimulate the endothelial cells to excessive or perverted function. Such may be the case with chronic infections, and certain cachexias, such as malaria. The chemical changes referred to—chiefly the lack of oxygen—have been supposed by Loeb to cause an increase of osmotic pressure in favor of the tissues over the blood and lymph.

A diminution of tissue elasticity and pressure is regarded by some as the main cause of edema *ex vacuo*, observed in the subarachnoid spaces of the brain and other portions of the central nervous system. Lymphatic obstruction does not usually cause edema on account of the free collateral circulation; but when large trunks are affected, or when there is

complete occlusion of the lymphatics of a part, a pure lymphatic edema may occur, and be hastened by increased lymph production. Bainbridge, summing up his conclusions, believes that cardiac dropsy is due to a disturbed relation between the vascular system and the lymph, while renal dropsy is due primarily to changes in the relation of the tissues to the lymph. He further adds that renal dropsy is due, first, to a scanty excretion of urine; secondly, to a retention of sodium chloride and possibly other salts, and, thirdly, to increased catabolism in muscles due to partial or complete loss of control over muscular metabolism by the kidneys. This catabolism brings about an accumulation in the muscles and tissue-spaces of waste products (metabolites). These metabolites, by a process of osmosis, attract water from the blood into the tissue-spaces. When the fluid in the tissue-spaces cannot be carried off by the lymphatics, edema appears.

The same writer explains the dropsy of anemia, first, by the low oxygen-carrying power of the blood, resulting in malnutrition of the capillary endothelium and consequent increased permeability; and, secondly, as in chlorosis, by the increase in volume of the blood, with resulting hydremic plethora. The venous and capillary pressure is raised, and increased filtration of lymph occurs.

The experiments and clinical observations of Widal and his associates led to a recognition of the influence of sodium chloride in the production of dropsy. Since edema fluid owes its molecular concentration, like other body fluids, mainly to its sodium chloride, a reduced amount of this salt in the body should hinder the

formation or accelerate the absorption of effusions. On the other hand, salt retention is believed to exist in some cases of nephritis, favoring edema. According to Widal, Lemierre and Cotoni, ingestion of large amounts of sodium bicarbonate checks the elimination of sodium chloride, and thus promotes retention of water.

Salt retention is an important factor in paroxysmal edema. Although the kidneys can take care of 2 to 3 Gm. (30 to 45 grains) of sodium chloride daily, any increase in the demand for this salt excretion actually reduces, at least temporarily, their capacity even below this amount. The marked therapeutic value of **reduced salt diet** and **free catharsis** is emphasized. W. W. Palmer (Arch. of Internal Med., Feb., 1915).

Sodium, and not chlorine, is the main factor in the production of sodium chloride edema. The potassium salt, potassium chloride, acts instead as a diuretic. Potassium carbonate greatly increases the excretion of chlorine and, while doing so, has little or no effect in reducing the patient's weight. Hausknecht (Ann. de méd., Dec., 1923).

Edema has multiple causes, any or all of which may be associated, combining to bring about a single phenomenon, *viz.*, increased capacity of the plasma to absorb fluid. The underlying disturbance may be an upset in the osmotic balance, the acid-base balance, the balance between the mineral constituents of the blood, or the fats and colloids in the blood. Mechanical factors are not the only ones involved in edema from circulatory disturbance. Conversely, vasomotor changes of the capillary circulation are present in edema of nervous origin, and even in angioneurotic edema, the edema is connected with the anaphylactic phenomena by a vasomotor link. Labbé and Violle (Ann. de méd., July, 1925).

In the edemas observed in nervous disorders, such as angioneurosis, neu-

ritis, neuralgia, hemiplegia, and organic disease of the cord, increased permeability of the capillary walls and transudation are regarded as direct causes. At the same time, imperfect absorption from vasomotor disturbances may have its influence, and changes in the tissues are in all probability involved. Whether the so-called hereditary edemas are due to congenital excess of vascular permeability is a question. Hektoen refers to the frequency of edema in arteriosclerosis; but inasmuch as edema often occurs without sclerosis, he suggested the term **angiopathic edema**. Thoma claims that in a certain proportion of cases angiosclerosis is a cause. Along with the actual condition of the arteries in these cases, we must take into consideration the condition of the heart and kidneys, and the direct processes, already mentioned, by which fluid escapes from the blood-vessels.

Martin H. Fischer, basing his conclusions upon experiments, holds that "in the variable affinity of colloids for water we have an explanation of many of those physiologic phenomena which are characterized by a storage or migration of water." He concluded, moreover, that alterations in the permeability of the vessel walls have never been demonstrated experimentally, and all efforts to produce states of edema through simple increase in blood-pressure have failed. The results of prolonged intravenous injection at high pressure of enormous amounts of various liquids are explained more easily, in his opinion, by changes brought about in colloids than through simple pressure effects.

The increased affinity of the colloids is caused by the fact that various sub-



stances (particularly acids) capable of greatly increasing the affinity of colloids for water are not removed as they should be, or are produced in abnormal amounts; and colloids having little affinity for water are changed into such as have a greater affinity. The former of these two propositions is the only one discussed.

To prove his proposition it must be, and can be, proved that protoplasm is colloidal; that in the variable affinity of colloids for water we have a force of sufficient magnitude to account without strain for the maximum amount of water ever found absorbed by tissues in a state of edema, and that conditions leading to an increased affinity of their colloids for water exist in the tissues under circumstances associated with the development of edema. With the exception of alkalis, acids, including carbon dioxide, are the most powerful substances thus far known for increasing the affinity of colloids for water, and it is either the retention or the abnormal production of acids in the tissues that causes the development of edema. Glaucoma, urticaria, and diapedesis are explained on this theory.

When edemas similar to those of heart lesions and thrombosis are produced in frogs, the acid reaction is so high that litmus is changed by the muscles. In nephritis, poisons are produced, and affect the tissues, altering their metabolism so that acids are produced which influence the colloids.

The writer regards edema as the result of imbibition of water into the cells outside of the capillary wall, due to insufficiency of oxygen. When pressure is made on an artery the capillaries dilate and the cells imbibe water to keep the capillary pressure up, for if the cells swell the capillary

is pressed on and narrowed, the venules are narrowed, and the capillary pressure is raised. Clinically he has noted disappearance of edema and healing of ulcers by means of a **tent bed** allowing the patient to breathe in comfort 30 to 40 per cent. **oxygen** for some days. Leonard Hill (Brit. Med. Jour., May 28, 1921).

There are 2 opposed theories concerning the origin of edema, *viz.*, increased permeability of the capillary walls, and change of the tissue colloids. The former is based on the fact that when edema fluid accumulates in the tissue spaces and serous cavities no tumescence of the tissue cells themselves can be demonstrated. In nephroses with edema, water ingested at once leaves the blood, suggesting an abnormal capillary permeability. Since edema is always much richer in electrolytes than the blood serum, simple diffusion and filtration do not suffice to account for the outflow and an additional driving force must be found. In the colloid theory the driving force is supplied by the tendency to tumescence (through increased affinity of the colloids for water in the presence of certain substances). In prædematous conditions, the writer maintains, there is an intracellular accumulation of water, and in actual edema there is also a pronounced tumescence of the connective tissue, in which the collagenous and elastic elements take part, and which is featured by thickening and tortuosity of the fibers. The general intumescence is preceded by intumescence of the capillary endothelial cells, resulting in impaired blood flow and checking of absorption. That intumescence of the capillary lymph channels occurs at the same time is indicated in that when edema sets in the thoracic duct and receptaculum chyli are nearly empty, while during absorption of the edema they are overfilled. In the writer's opinion, intracellular metabolism plays the main rôle in the absorption and elimination of water. He does not favor the view that the intumescence in edema is due to an excess of acid,

but regards sodium chloride as playing an important part in this connection. W. Huelse (Klin. Woch., Jan. 8, 1923).

Placing the gastrocnemius muscle of a frog in contact with plasma from edematous individuals resulted in an infiltration of the intermuscular connective tissue and the production of an actual edema. Labbé, Violle and Lelièvre (C. r. Soc. de biol., May 22, 1925).

*Epidemic Dropsy of India.*—This first attracted attention in Calcutta in 1877. After apparently subsiding, cases appeared in Calcutta in 1901, and in the following decade the disease was investigated by the government. There was a resemblance to beriberi. The main symptom was marked edema, mostly of the skin and subcutaneous tissues. The serous cavities may be invaded, and neuritis occur. According to Grieg, the malady resembles "ship beriberi," and also the "prison beriberi" of the early nineteenth century. It is non-infectious. Malnutrition from dietetic restrictions appears to be the cause of the disease.

The writer observed in Northern Africa cases of a low febrile state with vomiting and diarrhea, followed suddenly by anasarca, a peculiar eruption, acute anemia and intestinal disturbances. It is the first time, he thinks, that this epidemic dropsy has been known in northern Africa. The necropsy findings in the liver and kidneys resemble those of amyloid degeneration. He is convinced of the infectious origin. Leporim (Polí-clínico, Feb. 10, 1918).

**Pathologic and Microscopic Anatomy.**—The extent and situation of edema depends upon circumstances. It may manifest itself in a very limited space, as in urticaria and hydrocele, or involve nearly all of the organs and tissues of the body. The

transudate is found first in the lymph-spaces or interstices of the tissues, producing a more or less uniform swelling, which leaves a temporary indentation on pressure. Solid organs are rendered lighter in color, less dense, and moister than normal, and when the tissues are cut there is an exudation of liquid. The characteristic features of edema are best observed in the soft organs and submucous and subcutaneous tissues. The tissue elements are seen by the microscope to be more or less separated, and the cells may become diseased from pressure.

*Nature of the Fluid of Edema.*—The fluid is usually clear, colorless, of low specific gravity, and alkaline. It contains a smaller amount of proteids—especially fibrinogen—than blood-serum; also a few leukocytes and red cells. In serous cavities desquamated and degenerated endothelial cells and fat-drops are apt to be present, and milkiess may be due to precipitated albumin. Morbid products from the blood may be found. Inflammatory exudates are usually turbid, often bloody, of high specific gravity, rich in proteids, and sometimes contain a good deal of fibrinogen.

[In an interesting case of *pseudochylous ascites* reported by Henry, the fluid contained serum-albumin, serum-globulin, a small amount of nuclein, very little fat, a notable amount of lecithin, and traces of sugar, probably dextrose. The ash consisted of sodium chloride, phosphates, and sulphates. According to Wallis and Schollberg, the milky appearance of the fluid is due to a mixture of lecithin and serum-globulin. W. S. GORDON.]

*Results of Edema.*—These may be trivial, but at times are serious, as in edema of the larynx, lungs, brain, and other organs. Degeneration of

cells may occur, and connective-tissue changes, as in elephantiasis. Mechanical pressure may seriously interfere with the function of certain organs, while ischemia is common, and reduces the vitality and resisting power of the structures involved.

It is evident, from the various views expressed, that the mediate and immediate causes of edema are not fully understood; but much light has been thrown upon the subject, and we are nearer to an explanation of the complex processes involved in the production of dropsy. The consideration of the ordinary forms of edema and their *treatment* will be found under the diseases of the organs and structures in which it occurs. The subjects following may, however, fall appropriately under the heading of Ascites, treated below.

*Starvation Edema.*—The World War, through the widespread starvation it produced, gave rise to a large number of cases of this form of edema.

The edema of war or of prisoners' camps (U. S. Naval Med. Bull., July, 1918), occurred during the Napoleonic campaigns, the siege of Paris, and in the concentration camps during the Boer war, when it was known as epidemic edema (Maliwa). Falta, of Vienna, in a review of the subject, mentions that the disease was well known in Russia during famines before the war, and that the expression "swollen from hunger" was current in the affected districts. During the war the first record of the disease was in 1915 by Strauss, who described "the hunger disease" in Russian Poland and Galicia, where the poor were much exposed to war epidemics and had an insufficient and monotonous dietary. It has also been called "potato disease" and "salt hunger."

A form of edema was observed in 110 cases in certain towns in Poland from insufficiency of food following German occupation. The salient

symptoms were, besides the edema, muscular weakness, intestinal disorders, mental depression, dimness of vision, disappearance of sexual impulses, and alterations in the blood and urine. The edema was sometimes limited to the lower limbs, but more often spread over the whole body, involving the face, and especially the eyelids, sufficiently in some to interfere with vision. It sometimes led to bursting of the skin with serous exudation. The swollen, cold skin was painful when pinched up. The condition lasted 1 or 2 weeks in some, in others months, and sometimes recurred. Eight patients succumbed. Budzynski and Chelchowski (Jour. of Trop. Med. and Hyg., June 15, 1916).

The writer witnessed some 20 cases of bilateral enlargement of the parotid glands. The latter were at no time hard or painful, but rather soft and doughy. F. A. Park (Bull. Can. Army Med. Corps, Apr., 1918).

The symptoms of starvation edema consist of weakness, hypothermia, diarrhea, hard edemas, slow pulse in adults and rapid pulse in children. All patients have polyuria. The kidney function tests are normal. The urine often shows an excess of chlorides, magnesium, calcium, sulphur and phosphorus. The urea content is diminished, the ammonia and amino-acids increased, and the uric acid doubled. The blood shows lowered specific gravity, freezing-point and index of refraction. The red cells are diminished, and there is leukopenia. Inanition edemas are due to lack of fats, not of vitamins, for such edemas arose in war prisoners even when foods rich in vitamins, such as cabbage and honey, were given. S. Maggiore (Pediatria, Nov. 1, 1923).

Case of extreme edema in a young infant in whom a thin vegetable soup had been prescribed for diarrhea and continued by the mother for months. The soup was boiled down to one-half. Chloride retention is thought to have occurred. The child's trunk was poorly developed and the edematous legs suggested elephantiasis. The condi-

tion was corrected in a week by suitable diet. Jaureguy (Arch. Lat.-Amer. de Ped., June, 1925).

**TREATMENT.**—The curative treatment of edema resolves itself into measures calculated to counteract the cause. The condition itself, however, demands attention to give the patient relief and prevent the morbid effects incident to the presence in the tissues of what amounts virtually to a mass of foreign fluid. Rest, limitation of the amount of fluid ingested, and free movement of the bowels are the most important means in the treatment of obstinate edema. The bowels are acted upon by **Rochelle salt** in doses of  $\frac{1}{2}$  to 1 ounce (15 to 30 Gm.) in about 4 ounces (120 c.c.) of water. This may be preceded by a moderate dose of **calomel**. **Digitalis** combined with **squills** and **calomel** is very useful. **Theobromine** is most effectual in the dose of 10 to 15 grains (0.65 to 1 Gm.) three times daily, given dry on the tongue and washed down by a draught of water. The use of diuretics requires care, however, for the kidneys may be the seat of acute or subacute inflammation, conditions which limit the employment of these agents. **Caffeine** given in  $7\frac{1}{2}$ -grain (0.48 Gm.) doses 3 times daily for short periods has also given good results.

**Calcium salts** in large dosage have been found effective in some obstinate cases of edema; likewise, **novasurol**, which, according to Rowntree and others, is one of the most powerful diuretics known.

The writers used large doses of **calcium salts** (12 to 18 Gm. daily) in cases of massive edema of diabetic and nephritic origin. In 6 of 7 cases, most of which had been resistant to other

methods, the edema disappeared completely. In 1 case the edema disappeared, but the part played by the calcium was questionable. In 2 cases of nephritis, edema recurred later. None of these cases was complicated by significant myocardial damage, and in none was any other diuretic given. Small doses of calcium (1 to 3 Gm. daily) had little or no effect. In some of the cases edema was reduced by **calcium lactate**. In others **calcium chloride** seemed more effective. Large doses of calcium do not seem to increase the amount of serum calcium. In 1 case of diabetic edema the basal metabolic rate rose in  $2\frac{1}{2}$  weeks during the calcium treatment from — 13 to + 57. This effect did not occur in a normal person, nor in the other cases of edema. The high calcium content of milk may explain its diuretic action. Rockwood and Barrier (Arch. of Int. Med., May, 1924).

In 6 cases of severe heart failure in which edema was pronounced, satisfactory diuresis followed injection of **novasurol** in doses of 1 to 2 c.c. (16 to 32 minims). In another case there was little effect. In 1 instance **novasurol** was used tentatively after **digitalis** had already caused diuresis, without producing any appreciable additional result. J. H. Crawford and J. F. McIntosh (Jour. of Clin. Invest., Apr. 20, 1925).

Other drugs which may be serviceable, although confidence in them has been diminishing, are **sparteine sulphate** in doses of  $\frac{1}{4}$  to 2 grains (0.016 to 0.13 Gm.) and **apocynum**, 5 to 10 minims (0.3 to 0.6 c.c.) of the fluidextract (unofficial), 3 times daily.

**Urea** found useful as diuretic in heart cases with edema in which treatment of the heart has failed to remove the edema. In 8 cases with advanced heart failure, 30 to 60 Gm. (1 to 2 ounces) of urea a day was followed by a marked increase in urine output. The drug was especially serviceable where adequate water excretion was not maintained after the edema had

been dispelled by other means. In some cases it removed edema after other remedies had failed. Its effect was rapid but evanescent unless the drug was continued. The increase of urine output varied with the dose and closely paralleled the urea excretion. The daily urine output was kept nearly constant by continued exhibition of urea. J. H. Crawford (Arch. of Int. Med., Oct., 1925).

**Baths**—hot-air, vapor, or hot-water administered after the Mannheim plan—are a valuable auxiliary; so is **massage**, which seems to aid in the absorption of the effused liquid.

Evacuation of the fluid, by means of the **trocar** in ascites, **incision** of the legs—or on the dorsum of both feet as advised by Rolleston—in edema of the limbs, or again **Southey's tubes**, or **lymphangioplasty**, afford considerable relief, besides enabling the patient to increase his fluid intake, if previously restricted, thirst being sometimes very marked.

In **lymphangioplasty** for lymphatic obstruction causing chronic edema, as described by Guibé, silk is passed under the skin for long distances, the needle being drawn out at intervals and introduced again in the same hole. The operation gives good results in solid edema or, rather, elephantiasis; the only possible mishap is infection of the thread. In some of the cases on record the threads were withdrawn on this account, but after the lymph had become sterile they were reinserted with ultimate success.

**Deprivation of salt** is an important feature of the treatment, Widal, Lemierre, Javal, and others having found that edema could be produced in a suitable case by giving certain doses of sodium chloride. Some of the theories as to the mode of action of this salt are: (1) that the kidneys are diseased and partly impermeable to chlorides; (2) that the osmotic

power of the blood is sufficiently increased to enable its plasma to permeate to an abnormal degree the endothelium of the capillaries.

Be this as it may, a **salt-free** or **salt-poor diet** (see Treatment of Ascites for additional details) has been found materially to reduce the retention of fluids in the body.

In proper cases, **salt restriction** aids materially the elimination of retained sodium chloride and of water, generally causing a decrease of edema. Excessive salt restriction occasionally causes an increase or reappearance of edema. In very acute forms of nephritic edema, salt restriction should be combined with **drink restriction** so that the edema may be diminished or disappear. To test the renal capacity an occasional drinking or a salt day, singly or combined, is a useful means. This will also test the degree of retention of chlorides, or of retardation in their excretion. Persistence in salt restriction is desirable. Croftan (Jour. Amer. Med. Assoc., Feb. 17, 1912).

The writers, after observing 50 cases of cardiac dropsy, systematically treated with **reduction of fluids and of salt**, state these measures alone may restore conditions to clinically normal. They recall that the Karell treatment is on the same principle, but that it represents unnecessary deprivations. The writers give a light nourishing diet of 2000 calories but with only 700 or 900 Gm. of fluid and no salt in the bread. The patients do not object to this diet for a week. After this it is modified to allow 1500 or 1800 Gm. fluid and 2.5 Gm. salt with 2500 calories, but no meat. This fluid-poor and salt-poor diet is less distasteful the more pronounced the dropsy. **Rest** is an important feature of the treatment. Tchertkoff and Heim (Rev. méd. de la Suisse rom., Sept., 1918).

## ASCITES.

**DEFINITION.**—Accumulation of serous fluid in the peritoneal cavity, due

to, and occurring as, a symptom of diseased conditions of the peritoneum itself, such as inflammation, cancer, and tuberculosis; abdominal growths or structural enlargements pressing upon the portal veins; thrombophlebitis; obstructive disease, wounds, or rupture of the lymph- and chyle- vessels; affections of the heart, lungs, liver, and kidneys which produce either venous engorgement or altered states of the blood and consequent leakage from the vessels.

**SYMPTOMS.**—In moderate effusions the front of the abdomen is flat, and the flanks bulge when the patient assumes the recumbent posture. In the lateral posture the uppermost flank is depressed, while the front of the abdomen becomes prominent. When the effusion is large, the whole abdomen is distended and barrel-shaped, preserving its contour in any posture. The surface is uniformly smooth, unless there be encysted pockets of fluid. The skin is tense; linea albae may appear, and enlarged superficial veins, especially in portal obstruction, be observed. Fluctuation can be detected when a hand is placed on one flank, and tapping done on the opposite side by the other, the muscular wave being cut off by the edge of an assistant's hand placed firmly and vertically in the median line. Percussion gives dullness over the fluid and tympany over the intestines, the varying location of these signs depending upon changes in posture. Examinations should be made in the dorsal, lateral, standing, and knee-and-hand postures. Tyson has called attention to the fact that tympany in the flanks is sometimes noted even when the effusion is considerable.

In extensive ascites the upward pressure may seriously interfere with the

functions of the liver, lungs, and heart, while gastrointestinal disturbances, such as tympanites, nausea, vomiting, and constipation, are not uncommon. Albuminuria and frequent urination may occur. Ischemia is a necessary consequence of the pressure of the fluid upon the arterioles and capillaries.

**DIAGNOSIS.**—Catheterization eliminates a distended bladder. In hydatid, pancreatic, and ovarian cysts the fluid is at first localized at the diseased organ. Subsequently there is dullness over the center of the abdomen and tympanites in the flanks, exactly the opposite conditions to those in ascites. Pregnancy, especially with excess of amniotic fluid, may cause confusion in certain cases, but careful physical examination and the personal history can hardly fail to remove any difficulty in diagnosis. Hydronephrosis, when extensive, and when the urine contains no products from the kidney, can closely resemble encysted or even general ascites. The possibility of upward displacement of the liver and apparent enlargement in ascitic effusions should not be overlooked. Aspiration may be necessary in obscure cases in order to ascertain the nature of the fluid, or to outline the liver and spleen, enlargements of which are at times accompanied with ascites.

**PATHOLOGY.**—The character of the fluid varies according to the cause. It is usually of a low specific gravity (1010-1015), clear, straw-colored, and albuminous, undergoing at times spontaneous coagulation. Cancer and tuberculosis are apt to produce hemorrhagic effusions, while a milky color, though not common, may be produced by disease of the lymphatics, perforation of the thoracic duct, filariasis, or an excessive milk diet. The fluid in diffuse

septic peritonitis and the blood in ruptured tubal pregnancy possess their well-known characteristics, but are not ordinarily regarded as strictly ascitic effusions.

Study of the causes of ascites as found in 2217 autopsies which included 224 cases of ascites in which 1 quart or more of fluid was present. Cases of septic peritonitis and hemo-peritoneum being omitted, the bulk of the remaining cases were due to one of five causes: Cardiac weakness (89), nephritis (26), abdominal neoplasms (44), cirrhotic liver (23), and tuberculous peritonitis (15). Adherent pericardium (9), eclampsia (3), thrombosis of vena cava, portal and mesenteric veins (3), chronic fibrous peritonitis (3), uterine fibromyoma (3), intestinal obstruction (2), pancreatitis (1), ovarian cyst (1), acute yellow atrophy of liver (1), status lymphaticus (1). The causes of ascites in 3086 cases observed clinically at the Massachusetts General Hospital (1870-1910) were: Total cases of cardiac weakness from all causes 1397, renal and cardiorenal 665, cirrhosis of liver 325, tuberculous peritonitis 263, intestinal obstruction 86, ovarian cysts and tumors 63, uterine fibroma 55, neoplastic peritonitis 53, cancer of liver and lymph-nodes 30, cancer of intestines and lymph-nodes 56, cancer of pancreas and lymph-nodes 11, malignant lymphoma (thoracic and abdominal) 5, adherent pericardium 36, pernicious anemia 15, leukemia 12, syphilis of liver, etc., 4, thrombosis of vena cava, portal, and mesenteric veins 10. R. C. Cabot (Amer. Jour. Med. Sci., Jan., 1912).

A form of ascites common in India, assumed to be due to cirrhosis of the liver, is actually the result of a *chronic dysenteric peritonitis*, fibrosis of the peritoneum having been produced through irritation by the toxins of the dysentery bacilli. Usually there is a history of dysentery or severe diarrhea within a few weeks before the onset, and frequently agglutination in high dilution against the Flexner group of

organisms is found. The treatment consists of giving **saline laxatives** to expel the toxins from the bowel, and is not very effective at best. **Paracentesis** is to be avoided where possible, as rapid refilling occurs, with resulting increase of tissue starvation. J. W. D. Megaw and G. C. Maitra (Indian Med. Gaz., May, 1924).

**TREATMENT.**—The treatment of ascites consists in the removal, if possible, of the primary *cause*. According to indications, appropriate measures are addressed to the heart, lungs, liver, and kidneys. At the same time diuretics and, especially, hydragogue cathartics are employed. **Elaterium**, judiciously administered, and salines are valuable agents.

It is well to limit the drinking of **fluid**, and to support the patient's strength with **hematics** and **tonics**.

Case of ascites which was greatly benefited by the injection, into the peritoneal cavity, of **adrenalin** 1:1000 solution after other measures had met with but small success. The first injection consisted of 8 minims (0.5 c.c.) of the solution, which was given directly into the fluid in the abdominal cavity. In all, 9 injections were made, ranging from the smallest, 1 to 8 minims (0.6 to 0.5 c.c.), up to 2 c.c. (30 minims). At that time the ascites had entirely disappeared, and the patient was not troubled with orthopnea. T. M. Tyson and H. D. Jump (Therap. Gaz., Jan. 15, 1911).

[Whatever be the cause of ascites, relaxation of the arterioles with loss of the adrenal principle is an important feature. Injections of **adrenalin** intramuscularly, 8 minims (0.5 c.c.) gradually increased to 30 (1.8 c.c.), are often very efficient, besides increasing respiratory and cardiac activity. The remedy proves active sometimes where tapping fails, and is very helpful after it to prevent recurrence of dropsy. The effect may be kept up by **suprarenal gland** in 3-grain (0.2 Gm.) doses after meals.—Ed.]

Should these measures fail, tapping must be done under aseptic precautions, and repeated when necessary. The puncture is usually made in the median line midway between the symphysis pubis and navel, but can be made midway between the symphysis and anterosuperior spine, care being taken not to wound the intestine. The bladder should be previously emptied.

A **capillary tube**, the inner end of which is perforated laterally by many small holes for the distance of 1 cm., recommended. After the tube is introduced, the trocar is withdrawn and the tube is connected with a rubber tube and left *in situ* for several hours, the fluid draining off slowly. The method shortens the time consumed by the physician in paracentesis, and does away with the danger of collapse from the rapid reduction of intra-abdominal pressure. Buth (Deut. med. Woch., June 11, 1914).

Usually in true cirrhosis the portal vein is so tied up in adhesions that a true Eck fistula is not feasible. The writers devised a **modification of the Eck fistula** consisting of an anastomosis of one of the large mesenteric veins with the iliac vein at the point at which they cross. Edward Martin and J. E. Sweet (Jour. Amer. Med. Assoc., Oct. 16, 1915).

Two cases of ascites in which, after withdrawing a considerable amount of fluid, the writer introduced a **soft-rubber catheter** through the cannula and then withdrew the cannula, leaving the soft-rubber catheter *in situ*, making it fast externally by silkworm gut suture extending from the tube to the adjacent skin. In 1 of the cases, with ascites due to cardiac incompetence, at the first tapping 8 liters of fluid were removed; 3 weeks later 6 liters were removed, but only 10 days later he came in in as bad a shape as before. With the author's procedure, the flow ceased on the 6th day and there was a sudden increase in the

daily output of urine. Two months later he was hard at work, but he subsequently died of heart-failure, without a trace of ascites. O'Connor (Brit. Med. Jour., cited by Therap. Gaz., Apr., 1921).

In ascites due to portal obstruction from cirrhosis of the liver, or from compression in enlargement of that organ, **Talma's operation** (see p. 61, vol. i) should be considered, while the occasional good effects of incision and withdrawal of the fluid in tuberculosis of the peritoneum are to be borne in mind. Vidal and Martel anastomose the vena cava with the portal vein. Villard anastomoses the mesenteric vein with the ovarian. Tavernier, Talma, Morrison, and Lambotte resort to **omentopexy**.

The literature shows that about 40 per cent. have been cured of those to whom the **Talma operation** has been applied. It is not universally successful because the outcome depends on the functional capacity of the liver. **Continuous autodrainage** of ascites is still in its infancy, but the results already obtained are promising, especially as it requires such an insignificant operation in contrast to the laparotomy for the Talma operation. It is applicable for all forms of ascites, and the effect becomes evident at once. The drain-tube technique seems to have given the best results, but the best material for it is still a question. Autoplastic fascia tissue gave the best results in experiments on animals. A. Blad (Ugeskrift for Laeger, July 22, 1915).

In artificial **subcutaneous or retroperitoneal drainage** for ascites, **calf aorta** hardened in formaldehyde seems to answer the purpose perfectly. It heals in place and becomes organized without becoming obstructed. Possibly merely a large hole in the peritoneum might answer, without an actual drain. Schirmer (Corresp. Blatt f. schweizer Aerzte, Sept. 11, 1919).



**Omentopexy** has been successful in various forms of chronic ascites, including non-alcoholic hepatic cirrhosis, some alcoholic cases, and some cases with a positive Wassermann in which **antisiphilic treatment** was also used. The sooner it is performed when indicated, the better the prospects. Usually repeated tapping is further required after operation. Omentopexy is inadvisable in the extremely feeble and cachectic. F. P. Weber (Intern. Clin., 1, 88, 1924).

Case of recovery from ascites due to hepatic cirrhosis, after medical treatment had failed, following Talma's intramural **omentopexy**, combined with drainage. The cure has persisted 4 years. Tagliavacche (Prensa med. Argent., May 30, 1925).

The fact that celiotomy in tuberculous peritonitis has been found curative owing to the admission of air, *i.e.*, of oxygen, into the peritoneal cavity led Potain to try the use of **oxygen injections** into this cavity in *tuberculous ascites*, after withdrawal by puncture of the ascitic fluid. One thousand or more cubic centimeters of the gas can be injected without causing inconvenience other than temporary tympanites. It has also been found of value by Teissier in alcoholic cirrhosis.

In the treatment of tuberculous ascites by **heliotherapy**, the writer urges a reaction against the medical management of these cases that economically is often a hardship. The high sun exposure can be practised at home. Gelpke (Corresp. blatt f. schweizer Aerzte, Jan. 12, 1918).

In tuberculous ascites, the writer recommends the following: Painting stripes of **iodine** on the abdomen, leaving spaces between, which are also painted 3 days later, and so on alternately. In early cases, applying **colloidion** to a large area, then cotton and a bandage over all. The abdomen gradually becomes less tense due to absorption of the fluid. If the

fluid keeps on increasing, another procedure of considerable use is that of **adrenalin** injection, 3 to 5 c.c. (48 to 80 minims), into the ascitic cavity. **Strophanthin** has also been used to modify the vascularity of the serous membrane. An additional measure is that of **autoplasmotherapy**, the whole plasma being injected with all its formed elements. The resulting slow evacuation of fluid and polyuria favors the defensive action of immune elements contained in the liquid. M. V. Lefort (Arch. esp  n. pedi  t., Sept., 1921).

**Peritoneal fenestration** resorted to in 5 cases of tuberculous ascites, the fenestration being accomplished by excision of strips of peritoneum and suturing of the peritoneal margin outward, followed by a tight skin closure. Edema always appeared at the site of operation; in every case a marked improvement in the general condition resulted and there never was a recurrence of the ascites; nor did a post-operative ventral hernia ever form. In 1 case of peritoneal cancer the procedure also produced a marked improvement. The method has advantages over the customary broad laparotomy in that it is a less serious procedure, applicable in weak patients, and utilizes the healing powers of the tuberculous ascites, specific or non-specific, for the organism. F. Erkes (Arch. f. klin. Chir., Nov. 24, 1921).

Audibert and Monges introduced the use of **autoserotherapy** in the treatment of ascites. The method is as follows: After sterilizing the skin and instituting local anesthesia, the needle of a sterile hypodermic syringe of 10 c.c. capacity is introduced into the peritoneal cavity in the left side and a little of the ascitic fluid withdrawn. An assistant exerts pressure on the abdominal parietes if required. The syringe is then drawn out until its point lies in the cellular tissues, when the contents are reinjected. Progressively larger doses of ascitic

fluid are to be used (3, 5, 8, and 10 c.c.—48, 81, 130, and 162 minims). This procedure is repeated at intervals of six days and the treatment continued for two months. The method is painless and does not cause abscesses, local reaction, or fever. The authors claim that it produces lasting polyuria, retards transudation into the peritoneum, and permits of discontinuing the milk diet.

Undoubted case of cirrhosis in which **autoserotherapy** and other measures led to rapid absorption of an ascitic accumulation of 6 months' standing. Subcutaneous injections of 10 c.c. (2½ drams) of ascitic fluid were continued on alternate days. On the third day a free flow of urine set in, with the result that 11 days later the ascites had disappeared. Vitry and Sézary (*Revue de méd.*, Feb., 1913).

Autoserotherapy has been resorted to in the most varied forms of ascites, and the only contraindication is a purulent ascitic fluid. Small subcutaneous injections should be tried first. It is the only method permissible in tuberculous ascites, and here it is advantageous to combine it with laparotomy and proteolysis. In Laënnec's cirrhosis massive intravenous injections may be successful.

Marked diuretic action of **potassium chloride** observed in ascites and essential edema of renal origin, provided the cardiovascular apparatus was not involved. It must be given in doses of from 7.5 to 25 Gm. (2 to 6¼ drams) daily, and the system prepared by **restriction of the intake of salt**. The drawbacks are an intense laxative effect and the pronounced disturbance in the circulation which may follow even a relatively small dose when the heart is diseased. Blum, Aubel and Lévy (*Bull. Soc. méd. des hôp. de Paris*, Nov. 18, 1921).

A **salt-poor diet** has been found beneficial in a large proportion of cases. The blood in seeking to maintain its osmotic balance absorbs what

sodium chloride it can obtain from the tissues. The osmotic power of its serum being reduced, the latter leaves the circulation with less freedom, while the renal elimination of water is facilitated.

In a series of 14 cases of tuberculous ascites seen by the writer, only 5 were slightly benefited by diuretics. An extensive trial was then made with the **salt-free diet**. Normally, about 12 to 15 Gm. (3 to 4 drams) of salt are ingested, and an equal amount is excreted by the kidneys. If the patient takes only oatmeal, rice, stewed fruits, eggs, milk, and unsalted butter, the amount may easily be reduced to 2 or 3 Gm. (30 to 45 grains). The amount may safely be increased to 4 Gm. (1 dram) by allowing some meat, bread, and vegetables, all prepared with a minimum of salt. The patient stays on this diet for weeks; but occasionally a few days of normal diet should be interposed, to avoid monotony.

Eight out of 10 cases lost their ascites completely after salt-free diet for 5 to 7 weeks. W. Alwens (*Therap. d. Gegenwart*, Mar. 30, 1910).

The **Karell diet** has served the writer best. The patient receives daily at 8 A.M., 12 M., 4 P.M., and 8 P.M. 200 c.c. (¾ pint) of raw or boiled milk, warm or cold, according to taste. No other food or liquid should be given. This meets with violent opposition from the patient, owing to thirst, which is particularly tormenting during the first 3 or 4 days. The patient can rinse out his mouth with water, but he must swallow none. Hunger, if too urgent, may be relieved by giving a small piece of dry toast or zwieback with each portion of milk. During the first few days the patient requires continual encouragement to persist with the treatment, but the moral effect of the rapid loss of weight, as shown by daily weighings, together with the very evident decrease of the edema, prove sufficient argument to him, and no further complaint is heard.

The diet may usually be increased at the end of a week's time by giving a soft-boiled egg, without salt or pepper, at 10 A.M., and a piece of zwieback at 6 P.M. The next day an egg may be given at 10 A.M. and at 2 P.M., with a piece of white bread, and from now on food is gradually increased until a full diet is being taken. During this time the daily quantum of liquid should not exceed 800 c.c., ( $\frac{1}{2}$  quart) and this fluid should be in the form of milk, until the patient receives a full diet, when the milk may be discontinued and cocoa or tea substituted, the amount of liquid remaining the same, however. No more than 800 c.c. of fluid should be taken for from 2 to 3 weeks after the disappearance of ascites. During the treatment, which must be carried out with the patient in bed, the bowels must be kept open, and for this purpose laxatives in pill form are preferable to salines, merely because they require no water for their administration. Goodman (*Arch. of Internal Med.*, June, 1916).

Our Associate Editor, James M. Anders, holds that the **Karell cure**, which is much more used abroad than in America, is, in the opinion of His, not only effective in renal and cardiac dropsy, but alleviates the disturbance in breathing and other distressing symptoms not dependent upon the edema present in many of these cases. Prof. Anders deems it valuable before actual decompensation has taken place; for example, in cases of aortic valvular disease showing simply premonitory symptoms, associated perhaps with a mild grade of arteriosclerosis. After positive involvement of the kidneys and the presence of uremia it is altogether contraindicated. He does not advocate the use of the treatment in valvular disease with dropsy in which the kidneys are intact, but in all such cases there should be allowed more food of a higher caloric value, with aid to elimination by other means, such as rest, cardiac stimulants, etc. The use of iron is of advantage when administered in conjunction with the Karell cure.

### CHYLOUS ASCITES.

This is a form of ascites in which true chyle, a milk-like fluid, accumulates in the peritoneal cavity.

**SYMPTOMATOLOGY.**—Chylous ascites cannot as yet be deemed to possess a clinical history of its own, the chylous effusion being in most instances a cause of surprise when the ascites becomes sufficiently marked to demand evacuation by puncture. The abdomen presents the signs of ordinary ascites: enlargement, intestinal tympany, ready displacement of the liquid fluctuation, and dyspnea. The skin of the abdomen is often, however, the seat of supplementary veins, and the effusion not only tends to be quantitatively very great, but it is apt to return very rapidly and again in large quantities after puncture. The fluid is characteristic: it is white, lactescent, odorless and opaque, and fails to undergo putrefaction, the fluid itself, owing to its wealth in lecithin, being probably antiseptic.

Among the symptoms observed in such cases, ascribable in almost every instance to one of the numerous causative disorders, have been the signs of peritoneal involvement, and, independently of any such complication: fever, marked adynamia, premature senility, vertigo with tendency to syncope and finally, tinnitus aurium.

**DIAGNOSIS.**—Chylous ascites simulates fat-cell ascites, also met with in cancer and in tuberculous and chronic peritonitis. Its identity may be established, however, by the osmic acid stain, which colors the fat-cells black. The pus of purulent peritonitis, another source of con-

fusion, is readily identified microscopically.

**ETIOLOGY AND PATHOLOGY.**—Though not peculiar to them, chylous ascites is met with relative frequency in children. Among the causes that have been recorded have been inflammation of the thoracic duct; rupture of some chyle canal through traumatism or excessive venous distention; cardiac disorders capable of promoting the latter; pressure of a tumor upon the duct or transudation through its wall; intestinal sarcoma; chronic, cancerous, and tuberculous peritonitis; miliary tuberculosis; impaction due to filariasis, and other entozoa.

In a study of 126 cases collected from the literature, with 10 personal cases, Boston found as to exciting cause, 24 cases of chylous ascites complicating carcinoma; 17 due to tuberculosis; 11 accompanying cardiovascular conditions; 8 due to disease of the liver; 7 following puerperal sepsis, and 4 the result of congenital cysts. In addition there were 3 instances following infection with the *Filaria sanguinis hominis*. Obstruction to the thoracic duct was observed *post mortem* in 11 of the cases, and the duct or receptaculum was found to be ruptured as the result of traumatism in 7 of the cases. Sixty-one cases were females and 50 males.

Seven cases of chylous effusions.

The term chylous alone is sufficiently accurate and general to designate all milky effusions save those that can be shown to originate from lipemic blood. In each case the patient suffered from a lesion capable of producing effusions from the chyliferous vessels or the blood-vessels. In 1 case there were extensive tumor metastases. Another was a case of starvation anasarca after typhoid, the fluid probably escaping by filtration through a membrane made abnormally permeable by starvation and prolonged infection. Two cases had nephritis, but no evidence of disease of the chyliferous ducts existed;

possibly these were cases of nephritic lipemia. In 1 case an arteriovenous aneurism was present, the resulting high intravenous pressure causing back pressure in the chyliferous vessels and transudation of chyle. In 1 case there was a fibrosis of the intestines, causing stasis at the origin of the chyliferous vessels. Tests to determine the cause of the turbidity of the effusions in these cases showed the cause to be emulsified fat. M. A. Blankenhorn (Arch. of Int. Med., July, 1923).

Case of chylous ascites and chylothorax in a woman of 48 years, who had suffered for 2 years from weakness and abdominal discomfort. The abdomen enlarged and dyspnea developed. Percussion over the left iliac region elicited dullness and resistance, and the outline of a fluctuating mass. Laparotomy showed thin creamy fluid in the abdominal cavity and a large smooth mass involving the posterior peritoneum and the entire mesentery of the upper abdomen and extending into the left pelvis. Because of the extensive involvement of the entire mesentery, the mass was not removed. Four weeks later signs of fluid at the base of the right lung led to thoracentesis, which yielded 5 pints of chylous fluid. After frequent tapings of the abdomen the patient slowly failed. The autopsy showed a retroperitoneal lymphocytoma. B. L. Coley (Jour. Amer. Med. Assoc., June 21, 1924).

The disease cannot be said to present any special morbid anatomy, apart perhaps from its differentiation into its two types: true chylous and the pseudochylous ascites.

Report of 171 cases of chylous and pseudochylous ascites, including 3 cases coming under the personal observation of the authors. Milky ascitic fluid may be recognized in two main types—chylous and pseudochylous. The milky appearance of the latter is not due to free lecithin, fat, or a mucinoid substance, but to

a lecithin-globulin complex, which is held in suspension by the inorganic salts present in the fluid. By dialysis these inorganic salts may be removed, the lecithin-globulin complex precipitated, and the opalescence of the ascitic fluid disappears. The marked resistance of the fluid to putrefaction is due to the presence of lecithin. Wallis and Schollberg (*Quarterly Jour. of Med.*, part i, iii, 301, 1910; part ii, iv, 153, 1911).

Case of pseudochyloous ascites in a man of 60, admitted to the hospital with ascites, who in four months was tapped eight times, the smallest amount removed being 6 quarts, the largest 8 quarts. At the autopsy there was found a tumor at the pyloric orifice of the stomach cancerous in nature. The liver appeared perfectly normal. This showed how difficult it is in some cases to ascribe the disease to cirrhosis of the liver. The distinction between chyloous and pseudochyloous effusions is that the milky appearance of the latter is due, as in this case, to a combination of serum-globulin with lecithin or other lipid material. The remarkable resistance to putrefaction displayed by pseudochyloous effusions was due to lecithin, as proved by the fact that on the abstraction of the lecithin they rapidly decomposed. At autopsy there was no demonstrable obstruction of the portal circulation or alteration of the peritoneum, the chief lesion being a cancer of the pylorus. (See also page 189 for the nature of the pseudochyloous fluid.) F. P. Henry (*Med. Record*, June 17, 1911).

The writers made a chemical analysis of the fluid in a pseudochyloous ascites, collected at necropsy in a woman of 78 who had died of cancer of the gall-bladder with metastases. The most striking points chemically were: (1) The high content in lecithin; (2) the low fatty acid figure, and (3) the low cholesterol figure. Calcium in excess in protein combination does not appear to be responsible for any of the opacity of the pseudochyloous fluid. R. B. Gibson and C. P. Howard (*Amer. Jour. Med. Sci.*, July, 1923).

**PROGNOSIS.**—According to the researches of Wallis and Schollberg based on 171 cases, the prognosis is grave, the mortality reaching 66 per cent. in chyloous ascites and 70.4 per cent. in the pseudochyloous form.

**TREATMENT.**—This reduces itself to the elimination, if possible, of the cause and to symptomatic measures. **Tapping** is indicated, as it is in ordinary ascites. **Celiotomy**, especially if the case be due to tubercular peritonitis, may prove curative by admitting air, *i.e.*, oxygen, into the peritoneal cavity. The insufflation of **oxygen** through the cannula used for tapping might also prove advantageous in cases traceable to the same cause. In suitable cases **Route's operation**, vein transplantation, has proven curative.

The writer, in a personal case, operated as follows:—

Sept. 6, 1911: Operation. Ether anesthesia. Dorsal position. Right saphenous vein isolated and freed downward for 6 inches from saphenous opening. Branches tied and cut. Distal end ligated in two places and cut between. Skin incision extended to median line of abdomen below umbilicus, and peritoneum opened at this point. About 1 inch to right of median line a stab wound was made through the peritoneum and the end of the vein drawn through. Protruding end of vein split and the two flaps turned back and sutured with fine silk. Vein proved patent by probe. Peritoneum closed and skin closed over vein, which lay imbedded without kink or pressure in fat. Ascitic fluid only partly evacuated.

Sept. 17: Patient sitting up.

Sept. 21: Fluid in abdomen has returned and patient prepared for similar operation on left side.

Operation: Internal saphenous vein dissected out from saphenous opening to knee, tied and cut at distal end. Vein covered with gauze wet with hot

salt solution, and left muscle-splitting incision made in lower left rectus. Trapdoor flap of peritoneum turned back, and end of vein pulled through stab wound at its center and end split. The two flaps of the split end of the vein were then sutured back to the peritoneum with vaselin silk.

Patient recovered well from the operation, but by Oct. 1 the fluid had returned to a considerable extent and 8 quarts were withdrawn by tap. The left transplanted vein was apparently still patent, however, and the left leg became much swollen, but not red nor tender.

Oct. 13: Discharged relieved and left hospital.

Subsequent history: Patient resumed his work in a shoe factory in September, 1910, and has been perfectly well ever since. G. W. Morse (Boston Med. and Surg. Jour., Feb. 22, 1912).

Successful results obtained by **drain-  
ing** ascitic fluid in chylous ascites through the opening **between** the **fascial layers** of the thigh, where it is gradually absorbed. In a boy 8 years of age with chylous ascites, he used the **Lambotte-Handley** plan of **drain-  
age**. Six strands of No. 7 white silk 4 inches long were grasped in narrow blade forceps and thrust through the peritoneum to the outer side of the femoral vessels in the thighs and at the upper angle near the umbilicus. Five months later examination revealed no abnormality of the abdomen and the patient was in good health. F. Huber (Arch. of Ped., xxxvii, 600, 1920).

### ANGIONEUROTIC EDEMA.

**DEFINITION.**—An affection marked by transient circumscribed edematous swellings; closely resembling, if not identical with, giant urticaria; probably due to abnormal vasomotor influences, and frequently associated with more or less gastro-intestinal disorder.

**SYMPTOMS.**—The onset is sudden, and usually affects the hands, feet, genitalia, and the face, although

the lips, tongue, or glottis may be involved. Periodicity in the attacks has been noted. Redness, heat, itching, or urticaria may precede the attack. Vomiting, colic, and pain are common digestive symptoms, while hemoglobinuria and cardialgia have been observed, as well as affinities with Raynaud's disease and certain forms of severe purpura. Osler referred to a case with swelling of the whole arm. The condition is sometimes termed *Quincke's disease*.

*Blue edema* is a form of angioneurotic edema first described and named by Charcot in 1889. It occurs usually in association with hysterical forms of paralysis, and is characterized by suddenness of onset and local lowering of temperature, which may even precede its appearance. The edema generally affects only a single limb, and it is always situated at its extremity. Its duration is variable—sometimes it persists for several years, sometimes it can be made to disappear and reappear at will by hypnotism. Most authors agree that there is vascular spasm.

Case of hysterical edema in a woman aged 21 years who showed no hereditary antecedents, and in whom three years and a half after the loss of a sister and other troubles there developed a loss of voice, with changes in her character, mental depression, insomnia, loss of appetite, and incapacity to work. She lost 20 pounds in a few weeks. After a period of improvement in which the aphonia still persisted, pain developed in left knee with the appearance of a painful, purple, ecchymotic spot, making walking difficult. This soon disappeared. In July there appeared a similar spot on the back of the left wrist, with swelling of the articulation. The swelling and pain extended to the forearm and then to the hand. Contrac-

ture of fingers and wrist followed. A cast was applied under chloroform. The contracture lessened spontaneously during the patient's unconsciousness, and she spoke in a loud voice. Six weeks later the removal of the cast showed the swelling but slightly diminished and the fingers still contracted. X-ray examination showed the osseous system normal. In spite of electric and galvanic baths, application of collodion and methylene blue, and removal of bandages there was no change in the patient's condition. Glorieux (Jour. de Neurol., Feb. 20, 1911).

In a case described by the writer the hard edema covered the entire front of the trunk and neck like a sleeveless sweater, with 2 patches on the cheeks. The entire right side, besides, showed anesthesia. The patient was a soldier of 40, invalided home. The man had a history of measles, malaria and cholera. The edema developed almost all at once and shows a tendency to a blue tint, suggesting Charcot's *edème bleu des hystériques*. It is symmetrical and is accompanied by hemianesthesia, lateral hemianopsia and other nervous disturbances, including recurring aphonia. Carnelli (Policlinico, Med. Sect., 1918).

**Paroxysmal Form.**—Another type of angioneurotic edema of hysterical origin is characterized by the repeated occurrence of transitory edema affecting geometrical or segmented areas of the cutaneous surface. It is sometimes associated with disturbances of sensation quite hysterical in type.

**ETIOLOGY.**—Heredity is in some cases a marked predisposing cause. Emotional disturbances and cold may be influential. The immediate cause is supposed to be a dilatation of the blood-vessels, with transudation of serum.

According to modern observations, sensitization to foreign proteins, ali-

mentary or bacterial, is responsible for many cases, and the condition exhibits accordingly a kinship to asthma, hay fever, urticaria, etc.

Reference to the prevalent opinion that angioneurotic edema may result from either a congenital hypersensitiveness or a tendency to become artificially sensitized to a foreign protein. Some cases of allergic angioneurotic edema develop soon after eating the offending protein, with violent gastrointestinal symptoms and widely distributed urticaria, while others show no symptoms for some hours or often several days. In this class the areas are usually sharply localized, and skin tests are seldom positive. J. M. Phillips (Jour. Amer. Med. Assoc., Feb. 18, 1922).

[Harbitz wrote of "fatal familial angioneurotic edema," and cited a fatal case in which there was edema of the face and throat. A father and one grandfather died from the same affection, and other members of the family suffered. There are 170 cases on record, 36 dying from edema of the larynx. The disease may take the form of effusion into a joint. It is thought that anaphylaxis to some unknown substance is operative. W. S. GORDON.]

Two cases of *persistent hereditary edema of the legs (Milroy's disease)* with acute exacerbations were observed by the writer. Hope and French have summarized the characteristic findings as follows: Restriction of edema entirely to the legs; absence of any traceable cause, general or local; strong family predisposition; painlessness of the pale swollen legs (apart from the "acute attacks"); absence of constitutional symptoms; sharpness of limitation of the upper level of the edema; incidence in both sexes; permanence of the edema. No treatment seems effective, though the swelling may be held in check by **bandaging**. The disease does not shorten life. J. Phillips (Cleveland Med. Jour., May, 1914).

Animal experiments have shown that foreign protein always causes an

eosinophilia, which Schlecht ascribes to anaphylaxis. The writer observed eosinophilia in angioneurotic edema, and regards it similarly as of anaphylactic origin. A patient of his was subject to attacks of edema about the eye, tongue and larynx, with substernal oppression. With the attacks, eosinophilia rose to 20 per cent., increasing for 6 to 8 days after each attack, then declining to about 8 per cent. The absorption of the serum extravasated during the attacks is regarded as the cause of the eosinophilia. Injections of adrenalin reduced the eosinophilia temporarily. M. Ganslen (Med. Klin., Oct. 6, 1921).

Study of 125 cases of edema from vascular spasm. One woman, following an antitoxin injection, had developed severe multiple anaphylactic manifestations, some of which continued for years. Aside from mental or mechanical causes, important causal influences seemed to be exerted by seasons and atmospheric changes. The edema appeared oftenest in the spring, and between 3 and 6 A.M., *i.e.*, at the time of the maximal conduction of electricity in the air. Some cases in the series had severe attacks of abdominal pain or were complicated with nephritis. In cases with chronic edema the affected areas showed extreme sensitiveness to pressure or pinching. In acute edema there was local itching, and the majority of such cases had a history of urticaria. G. Schorer (Schweiz. med. Woch., Apr. 16, 1925).

**PROGNOSIS.**—The disease is often obstinate, being apt to recur at intervals of several weeks, but life is not endangered unless the larynx be involved.

**TREATMENT.**—Especial attention should be directed to the gastrointestinal tract; general hygienic rules should be enforced, and tonics administered when required. Coincident disorders should be rectified. Osler called attention to the value of large

doses of **strychnine** and the prolonged use of **nitroglycerin**. **Atropine** and **adrenalin** have proven of some value during the attacks. When the larynx is involved, **scarification** of this organ or even **tracheotomy** may be required.

**Foci of infection** should be sought for and **removed**. Skin tests for hypersensitiveness to foreign proteins may serve as a basis for treatment, *e.g.*, by adjustment of diet. **Vaccines** made from any organism found may likewise prove useful. (For further details, see the articles on Anaphylaxis, Asthma and Hyperesthetic Rhinitis.)

Excellent results were obtained from **adrenalin**, giving 4 minims (0.25 c.c.) of the 1:1000 solution. When given in the first stage of numbness and itching the injection would abort the attack at once. Later the writer gave **adrenal gland**, 3 times a day. The attacks were diminished in frequency and severity, then ceased. J. A. Codd (Brit. Med. Jour., June 16, 1917).

The writer obtained favorable effects in 3 cases from desiccated **thyroid gland**,  $\frac{1}{2}$  grain (0.03 Gm.) three times a day increased to four doses daily. Dryland (The Medical Press, Aug. 8, 1917).

Most cases in adults are due to bacterial sensitization. In 1 case chronic urticaria and angioneurotic edema disappeared after 2 operations on the left antrum and frontal sinus. Several cases recovered after **tonsillectomy**. The sensibility often develops during an acute infection, after subsidence of which a residual focus is left, causing chronic or recurrent symptoms. H. B. Barber (Guy's Hosp. Rep., Jan., 1923).

### EDEMA NEONATORUM.

This rare condition, more or less general, and observed in the first few days or weeks of life, occurs in weak infants. The swelling is usually con-



finer to the lower portions of the body, and the lower limbs. Weakness of the right heart is supposed to be one of the main causes. The differentiation from sclerema, as given by Fairbanks, is as follows: "In edema the skin is usually soft; it may or may not pit; it can be pinched up in folds unless the edema is extreme; rigidity of the body is not present; the skin, when cut at autopsy, exudes serum, and when examined under the microscope large spaces are seen where the connective tissue has been forced apart by the fluid. In sclerema the skin is hard, in severe cases as if frozen; it never pits; it cannot be pinched up, but seems as if it were fastened down to the underlying parts; there is more or less rigidity of the entire body; there is no exudation of serum when the skin is cut, and when examined in section it and the subcutaneous tissue are seen as a dense mass in which fibrous tissue predominates and no dilated interconnective-tissue spaces are present. The only way in which the two affections are similar is that they both occur in feeble and often premature infants in the first few days of life."

Anemia, marasmus, heredity, toxemias, nervous influences, cold, and other factors have been supposed to be more or less operative as causes of this condition, but the exact etiology, as applied to certain groups of cases, is not yet determined.

Case of extreme congenital generalized edema in a premature infant. The mother had shown a tendency to edema during the pregnancy, having had an acute nephritis as a complication of diphtheria 3 years previously. Bazán (*Semana méd.*, July 9, 1925).

The treatment is governed by the symptoms and the general indications.

### IDIOPATHIC OR ESSENTIAL DROPSIES OF CHILDHOOD.

The characteristic feature of this condition is the appearance of edema in one or more parts of the body without albuminuria or sedimentary evidence of organic disease of the kidneys: without clinical or postmortem evidence of organic disease of the heart or kidneys. It may occur in children of any age, but is not limited to childhood. It occurs in children who previous to and during its presence are otherwise well; or it occurs, accompanied by symptoms more or less peculiar to it, in children previously and subsequently well; or, finally, it occurs immediately preceding, accompanying, or immediately succeeding some disease other than the organic conditions above mentioned.

The series of coincident symptoms of the second class is only collectively, not individually, peculiar to the affection. The disorder may be acute, subacute, or chronic. It cannot, therefore, be said, in any given case, that the edema is positively primary or definitely secondary. The time of year seems to have an influence upon its occurrence only in so far as the seasons are accompanied by those factors that are of undoubted importance in the etiology, such as extremes of temperature, especially cold, or the prevalence of gastrointestinal derangements, with their accompanying toxemias and conditions of low vitality. In 25 per cent. of the cases anemia was present; in 43 per cent., gastric or enteric disturbance, usually diarrhea; in 15 per cent., marked emaciation; in 15 per cent., subnormal temperature; in about 7 per cent., urticaria, and in 4 per cent., purpura. The temperature was normal in a few

cases. Symptoms pointing to edema of the larynx or throat occurred in 5 per cent. In 2 cases of supposed meningitis the symptoms may have been due to cerebral edema. The most common associated feature was gastrointestinal disorder (Fairbanks).

Edema may complicate the clinical picture of "flour injury," *i.e.*, that condition due to a diet composed chiefly or entirely of starches. This form of complication occurs especially where the flour is given in a salt-rich diet, as bouillon, milk, etc., and the edema may resemble that of a nephritic patient, although the urine is usually negative (Hess).

[Under this heading may be mentioned a group of cases reported some years ago by Edgeworth. The patients were 6 children, of healthy parentage, who developed subcutaneous edema in from one to sixteen weeks after birth. One case, with facial involvement, recovered; 5 died in from one to sixteen weeks. In at least 3 no albumin was found in the urine, and in 2 cases no postmortem evidence of nephritis could be discovered. All had more or less of diarrhea. In one case calcium chloride lessened the edema. Toxins acting upon capillary vessels defective from birth were supposed to be the cause of the edema.

Hume has laid stress on general edema following gastroenteritis in children. In the group of cases he describes, there were no evidences of heart or kidney lesions. Salt metabolism was the same as in healthy children. In 2 cases there was an abnormal degree of fibrosis in the medulla of the suprarenal gland. The vascular condition was improved by the injection of **epinephrin**, improvement being more rapid with than without this substance. He thinks the edema may be due to the influence of gastrointestinal toxins upon the suprarenal medulla. There might be an absence of suprarenal secretion. Or, the toxins may act directly upon the cells of the capillary vessels. W. S. GORDON.]

An infant presented marked edema of the legs, abdomen, back and face.

The extremities were very cyanotic, and there were disseminated ecchymoses and petechiæ. The child died in a few hours. At necropsy, thrombi, some calcified, were found in the left kidney, with disseminated collections of normoblasts. P. Gautier (*Arch. de méd. des enf.*, June, 1924).

Joseph reported the case of a boy of 5 years who, whenever he walked in the cold air, developed an edema consisting of small, discrete, somewhat itchy elevations on the face and arms. Along with the edema appeared abdominal pain and, on prolonged exposure, hemoglobinuria. The disturbance would disappear upon his remaining indoors. The patient's 8-year-old cousin was similarly affected.

During an epidemic of gastroenteritis among babies, as described by De Wolf, 13 cases of edema made their appearance in 11 days. The patients all had gastroenteric trouble either immediately preceding or at the onset of the edema. The symptoms were as follows: Face pale, pasty-looking, apathetic, depressed; temperature subnormal; skin dry, soft, deeply pitting on pressure. In a number of the cases the edema was intense, and would rapidly change from the face to the legs or other parts of the body and *vice versa*. The weight increased before or with the appearance of the edema and decreased when the edema subsided. The urine in 9 cases contained albumin, but the casts were very few or none. One case which died while the edema was present showed normal kidneys at autopsy, so the kidney trouble was evidently not primary. The children were in 3 different wards on different floors, attended by different nurses, yet developed the trouble simultaneously. All of the patients referred to were artificially fed.

In the Manchester Children's Hospital, during the autumn, it is fairly common to find infants who have edema of the feet and hands. The edema usually appears toward the end of an attack of gastrointestinal catarrh, when the vomiting and diarrhea are getting better.

Edema is bilateral and attacks the dorsum of the hands and feet, and occasionally the face becomes puffy,

giving the appearance of a renal condition. The heart and lungs are usually found normal. The urine is high-colored, acid, and foul-smelling, and contains a few leucocytes, but no blood or casts. Small amounts of albumin are found at times, but, while there is no nephritis, there is renal inadequacy and the child is suffering from toxemia. Necropsy shows no change in the kidneys, except slight cloudy swelling in the tubules. The blood in these cases shows a high proportion of hemoglobin and a slight increase in the number of red blood-cells. The circulation is not especially feeble. Edema, when it occurs in the course of gastrointestinal diseases, is a serious symptom, although quite a large number of cases recover. Hugh Ashby (Practitioner, May, 1911).

The affection is supposed by the majority of observers to be of nervous origin. The cases of intermittent hydrops of the joints are probably due to the same cause. Certain cases of ascites occurring in young girls and unaccompanied with marked general disturbance, except, in one or two instances, transient fever, vomiting, and loss of appetite, have been reported. In 4 of the 6 cases mentioned by Quinke the condition disappeared with the onset of the menses.

**TREATMENT.**—Besides treatment of the underlying conditions, the measures indicated in this disease should include a diet in which the **proteids** are liberally represented, mainly to enhance vascular tone. Of the diuretics **potassium citrate**, with small doses of **digitalis**, have given the best results. Morphine is not only useful to prevent the abdominal symptoms which are often severe, but also to diminish the effusion. **Mercury biniodide** in small doses or the **iodides** are indicated when a his-

tory of syphilis, inherited or acquired, can be traced.

The prognosis is usually good in the essential edema of children, edema of the larynx being the only cause of death. Abdominal symptoms are often severe. **Morphine** seems to be the only agent that helps. **Scarification** and application of **supra-renal extract** to the edematous parts is recommended in edema of the larynx. Tracheotomy may be necessary. Avoidance of predisposing articles of diet and relief of constipation are prophylactic measures. Schwarz (Amer. Jour. of Obstet., Oct., 1908).

Five cases of edema and anasarca in infants cured by **specific treatment**. In one case there was a clear history of inherited syphilis. In another the edema was traceable to a liver affection, and in another to septicemia. The other cases demonstrate that edema and anasarca are liable to result merely from gastrointestinal disturbances, even when it is apparently mild. The anasarca of digestive origin is the result of well-defined lesions in the organs involved, for which the gastrointestinal affection is primarily responsible. Lereboullet (Annales de méd. et chir. infantiles, Feb., 1909).

[E. Favel (Correspondenz-Blatt für schweizer Aertze, Basel, August 10, 1911) describes a method for **subcutaneous drainage** in ascites. He uses a glass spool, with broad ends and a caliber of 1 cm., one end of which is worked into the peritoneal cavity. A hole to support the other end is made in the subcutaneous tissue. Not even local anesthesia is necessary. The omentum should be kept out of the lumen. W. S. GORDON.]

When there is edema of the larynx scarification with **epinephrin solution** applied locally to cause contraction of the edematous tissues is necessary to prevent asphyxia. The bowels should be kept free by means of **saline laxatives**. As in other

forms of edema, a **salt-poor diet** is also of material prophylactic value.

In infants who are the subjects of acute or chronic disturbances of nutrition, excess of salt may cause edema, even when there is no evidence of disease of the kidneys or heart. The writer records a case of this type in a boy 5 years of age. It was found that the broth given the child was very salty and had caused considerable thirst. A **diet poor in salt** was ordered, and in 3 days the edema had lessened considerably, with later complete restoration to health. F. Hamburger (Münch. med. Woch., Nov. 21, 1911).

Cowie has divided ascites in infants into 2 groups: (1) during the nursing period, and (2) in later infancy. In a case observed by the writer, belonging to the first group, the child being 4 months old when the fluid was first noticed, it was removed by 31 tapings, varying from 350 to 1250 c.c., or a total of 24 quarts in 2 months. Fluid was at first clear and straw-colored, later milky and chylelike, at 1 time 1.45 per cent. of fat (Babcock method) being found. There was no demonstrable causative disease condition, no general edema, and the child completely recovered, gaining 2320 Gm. in weight within the 3 months of illness. Urine showed a high chlorine content throughout, but sodium chloride was restored to the diet without untoward effects. C. A. Scherer (Internat. Clin., 2:244, Series 32, 1922).

Description of a syndrome termed hypogenital ascites, occurring in young patients with evidences of hypogonadism, thymic diathesis or pluriglandular disorders, in particular hypothyroidia. The condition is distinct from tuberculous peritonitis in that general health is good, there is no abdominal tenderness or fever, and the tuberculin tests are apt to be negative. **Thyroid and gonad extracts** proved beneficial. Stanganelli (Rif. med., Jan. 11, 1926).

WM. S. GORDON,  
Richmond, Va.

**ASPHYXIA.** See RESUSCITATION.

**ASPIDIUM** (U. S. P.), or **MALE FERN**, is the rhizome of the *Dryopteris filix-mas*, a fern found in Europe, America, Asia, and some parts of Africa.

Aspidium contains, among other more or less active constituents: *Amorphous filicic acid*, *aspidin*, *aspidinin*, *albaspidin*, *flavaspidic acid*, and *filmaron*, to which the therapeutic properties of the drug are ascribed. There are also a volatile and a fixed oil, tannin, etc.

The value of the oleoresin of male fern depends on the presence of aspidin, as well as that of filicic acid. Out of 11 preparations examined, 6 contained aspidin in large proportion (2 to 3 per cent.), while filicic acid was absent; 4 contained filicic acid, but no aspidin, and 1 contained small quantities of both. These results show that a high content of aspidin excludes the presence of filicic acid, and *vice versa*. An oleoresin containing principally aspidin is decidedly preferable to one rich in filicic acid. Boehm (Südd. Apoth. Zeit.; Bull. of Pharmacy, vol. xxi, No. 11).

The main drawbacks of male fern are its varying strength, disagreeable taste, and irritating properties manifesting themselves in vomiting and intoxication. The principles occurring in male fern were carefully tested by the writer. He found that all the active properties were contained in the amorphous acid filmaron, which constitutes about 5 per cent. of the extract. Filicic acid and albaspidin are also anthelmintic, but to a less extent, and are also less abundant in the extract. The average dose of filmaron is 0.7 Gm., and patients very rarely experience other after-effects besides slight nausea or transient abdominal cramps. In efficacy it seems to be almost equal to the fresh extract from the rhizome. A. Jaquet (Therap. Monats., Aug., 1904).

**PREPARATIONS AND DOSE.—**

The official preparation of aspidium is the oleoresin: *oleoresina aspidii*, a thickish, green fluid having a bitter, disagreeable and even nauseous taste. The dose is from 15 to 60 grains (1 to 4 Gm.). This may be administered in capsules previously dipped in a solution of formaldehyde or coated with keratin, or in pills dipped in salol to render them insoluble in the gastric juice and prevent irritation of the stomach. It may also be given in emulsion,—the form in which it is generally used for children. Formulas for emulsions are given below, under Therapeutics. Aspidium should never be administered with castor oil; filicic acid being soluble in the latter, toxic phenomena may result.

A dangerous combination recently, a prescription calling for the following ingredients, was presented to an eastern pharmacist for dispensing:—

℞ *Oleoresin of male fern* ..... 1 dr. (4 Gm.).  
*Oil of turpentine*. 30 grs. (2 Gm.).  
*Castor oil* ..... 2 oz. (60 Gm.).

M. Sig.: Take at one dose.

The presence of castor oil in the above mixture would cause the prescription to be a dangerous one, since the filicic acid, one of the poisonous constituents of male fern, is dissolved by the castor oil, its absorption being thus promoted. The oleoresin of male fern should never be prescribed with castor oil or other oily substances; in some European countries there is a legal prohibition against dispensing extract of male fern in combination with castor oil. F. J. Wullung (*Journal-Lancet*, Jan. 15, 1911).

**PHYSIOLOGICAL ACTION.—**

Aspidium is toxic to all entozoa, and is probably the most reliable agent at our disposal to destroy any of the varieties of *tenia*, or tapeworm.

Study of the physiological action of male fern by means of the "demarkation current" of DuBois-Raymond, which occurs when one end of the muscle is suspended in a solution of the drug to be tested. It was found that, of the different principles and their derivatives, phloroglucin, filicinic and butyric acids were inactive; of the remainder, the filicinic acid butylamin was least active, then followed aspidinol, flavaspidic acid, albaspidin, and finally filicic acid as most potent. For protozoa the order of toxicity was somewhat different: thus,—albaspidin, filicic acid, flavaspidic acid. A number of other invertebrates were tested, from celerata to crustaceæ, and in all, with the exception of certain echinodermata, the great virulence of male fern was demonstrated. Its active principles proved to be strongly poisonous for all kinds of organized plasma, but more particularly for muscle-tissue. This was most beautifully shown in the case of worms, and the empirical use of male fern as an anthelmintic finds its scientific proof in these experiments. W. Straub (*Archiv f. Exper. Pathol. u. Pharmacol.*, Bd. xlviii, S. 10, 1902).

Aspidium is a powerful irritant of the gastrointestinal canal, and its use in excessive doses gives rise to toxic phenomena, even though its absorption is slow. Fortunately, doses sufficient to destroy the parasite are harmless to the patient—unless administered with oil—and are readily eliminated from the intestine. The action of aspidium on the spinal cord has been compared by Cushny to that of strychnine, since toxic doses cause a distinct increase of reflex excitability. The dominant symptoms, according to Prévost and Binet, are paralysis and rigidity of different muscles, including those of the heart and intestines. Paralysis of the heart

is the usual cause of death, the organ being found after death in a condition of firm contraction and non-irritable. Peristalsis is almost entirely suppressed in the rabbit, cat, guinea-pig, and pigeon.

In experiments performed by Georgiewsky, animals poisoned acutely with large doses failed to show post-mortem changes capable of accounting for death. Animals poisoned gradually, however, showed marked blood-changes: diminution in the number of erythrocytes and the proportion of hemoglobin, even though the animals had lost considerable serum through numerous alvine discharges, thus increasing the viscosity of the blood. Though the tissues in general were normal, the liver and kidneys were found to contain considerable iron, doubtless originating from the broken-down red corpuscles—the cause of jaundice in cases of poisoning.

[Acute poisoning is accounted for, from my viewpoint, by reflex constriction of the arterioles through the sympathetic system, and the resulting blocking of the tissue circulation thereby. The muscular rigidity would then be a result of the accumulation of toxic wastes which follows deficient circulation of arterial blood in any organ. The hemolysis of slow poisoning corresponds with that awakened by many agents which promote the formation of antibodies which, produced in excess, destroy not only the antigen (the aspidium in this instance), but also the blood elements. C. E. DE M. S.]

**ASPIDIUM POISONING.**—Text-books of pharmacology lay but little stress upon the dangers of poisoning by aspidium, but men who are in the practical field speak otherwise. Grawitz, for example, has emphasized these dangers. Nausea, faintness, tremors, drowsiness, tinnitus aurium,

lassitude, and icterus are not uncommon, while vomiting, profuse sweating, purging, severe abdominal pain, diminished urinary flow with albumin and hyaline casts, twitching of the muscles, tetany, delirium, coma, and death have not infrequently occurred as a result of excessive doses. In a series of 78 reported cases of aspidium intoxication studied by Sidler-Huguenin (*Correspondenzblatt für schweizer Aerzte*, Nov. 17, 1898) 12 terminated fatally. In the cases saved nervous disorders may follow.

Case in a man of 38 who took 8 Gm. (2 drams) of extract of male fern with 16 Gm. (4 drams) of castor oil, the combination being a proprietary mixture (Tritol-Stark), to expel a tapeworm. The man believed that he had the parasite and took the medicine without consulting a physician. The drug caused vomiting, violent clonic and tonic cramps, irritation of the kidneys, and fever, but the eyes did not seem to be affected. The tendency to circulatory disturbances was seriously aggravated, the toes were congested and numb, and there were blue patches on the leg. The man had to stay in bed for six weeks with varying degrees of pain in the leg, and he was left with serious paresis of the limb, the type suggesting poliomyelitic paralysis. Magnus-Levy (*Berl. klin. Woch.*, March 27, 1911).

Optic atrophy, with typical gray or white discoloration of the optic nerve and contraction of the retinal arteries, has been observed after severe intoxications, while transient amaurosis and amblyopia, with dilated non-reacting pupils, are comparatively frequent. In 44 out of Huguenin's 78 cases temporary or permanent disease of the optic nerve was the main lesion. A suggestive fact in this con-

nection is that castor oil had been given along with the extract in 57 per cent. of the cases.

Case of a woman aged 35 who thirteen years before had been treated with extract of male fern for tapeworm, with success. Portions of *Tænia mediocanellata* being found again in her stools, her own medical attendant ordered her extract of male fern 8 Gm. (2 drams), calomel 0.8 Gm. (12.3 grs.), divided into 16 doses, placed in capsules, 2 of which (= 15.4 and 1.5 grs.) were to be taken every ten minutes. After one and a half hours from the beginning of the treatment, she passed an entire tapeworm, but shortly afterward she experienced general sensations of weakness, and was attacked by typical tetanic spasms. These spasms could be stopped by firm pressure on the large vessels and nerves of the arm. Trousseau's and Chvostek's phenomena were well marked. Recovery was complete in three weeks. No signs pointing to involvement of any organ could be detected during the course of the tetany. Treatment consisted of **warm baths** and **hot packs** to the **extremities**. Dammer (Münch. med. Woch., Nov. 13, 1900).

Case found in deep coma which had been preceded for two days by headache, vertigo, apathy, and complete anorexia. The diagnosis at first sight seemed to rest between epilepsy and apoplexy. A hasty examination showed a rapid, regular, but thready pulse, wide pupils, increased patellar reflexes, and a tonic spasm of the entire body, especially of the arms. The rapid reaction on stimulation made it more and more likely that the case was one of intoxication. It was then found that the patient had swallowed about 2½ drams (10 Gm.) of pure extract of male fern for an alleged tapeworm. W. Gotthilf (Münch. med. Woch., Bd. xlviii, S. 1096, 1901).

Case of a man aged 52 years who took 12 capsules of ethereal extract of male fern. He got rid of the tape-

worm, but an hour later fainted. All attempts to bring him to proving fruitless, the patient was given **lemon juice**. He immediately rallied, vomited, and rapidly improved. A slight syncope having occurred an hour and a half later, the same treatment, followed by a second evacuation, effected a complete cure. Anonymous (Medical Bulletin, Nov., 1907).

### TREATMENT OF ASPIDIUM

**POISONING.**—As a light case of poisoning frequently develops into a serious one, the use of aspidium should be discontinued when any untoward sign appears: headache, nausea, twitchings, etc. Aspidium being slowly absorbed, a purgative is indicated, but castor oil should be avoided, as it would aggravate the case. **Citrate of magnesia**, by causing watery stools, will best clear the intestinal canal of what amount of the drug it may contain. Hypodermic injections of **ether**, **camphor**, aromatic spirit of **ammonia**, with hot **coffee** by mouth or rectum, or other stimulants, and hot (108° F.) saline solution **enteroclysis**, are indicated.

**THERAPEUTICS.**—Aspidium is now used exclusively as a remedy for **tapeworm** and **Ankylostoma duodenale**. Special care is necessary, and the dose administered should be especially small in young, anemic, and badly nourished subjects. Intestinal, renal, and cardiac diseases also enhance the liability to toxic effects. Chronic alcoholism, chronic appendicitis, and lactation are also contraindications. Castor oil should not be used either before, during, or after the administration of aspidium.

There are various methods of using the drug. Most authors favor a preliminary purgative and the withholding of food some time before

administering the vermifuge. Ewald, however, holds that this practice favors absorption of the drug and facilitates the production of toxic effects. He resorts to no preliminary treatment except, perhaps, a mild saline aperient, followed by coffee, and the dose of the extract used by him never exceeded 30 grains (2 Gm.). One hundred cases treated in this manner proved entirely successful, and failed to show the least untoward effect. Boas also ignores the preliminary measures and uses smaller doses than are usually recommended.

The writer's method is as follows: He gives, fifteen minutes after a breakfast of coffee with zwieback, the following formula, which has acted well in his hands: Fresh ethereal extract of male fern, 2 or 2½ drams (8 to 10 Gm.); powdered jalap, 7½ grains (0.5 Gm.); simple syrup, enough to make 1 ounce (30 c.c.). This mixture should be well shaken. The parasite usually appears in three to four hours. Schilling (Therap. Monats., Bd. xxii, S. 187, 1908).

Yet, the impression prevails, and probably on correct premises, that where there is no preliminary abstinence from ordinary food the parasite is protected by the latter, and the remedy fails to produce its toxic effect upon it. It is customary, therefore, to keep the patient on a light diet a couple of days, and if constipation prevails to administer a purgative. The oleoresin is then administered in capsules, 5 or 6 grains (0.3 to 0.39 c.c.) in each, giving 1 capsule every ten minutes until the total amount to be administered—30 or 45 grains (2 to 3 Gm.)—has been given. One hour after the last dose, a bottle of citrate of magnesia is administered, and the patient is instructed to defe-

cate in a vessel containing water, so as to prevent breaking up the parasite. Where this procedure does not succeed, it is because mucus in large quantities protects the worm; the use of Carlsbad salt before resuming the treatment is then indicated.

The duodenal tube recommended for the introduction of the vermifuge, as it removes all risk of intoxication by permitting smaller dosage and also avoids vomiting. A purgative having been given the evening before, the tube is introduced next morning, ½ of an infusion of senna—5 Gm. (75 grains) in 50 c.c. (1⅔ ounces) of water—injecting, and ¼ hour later, the rest of the infusion along with extract of male fern, 2 Gm. (30 grains), and extract of pomegranate bark, 4 Gm. (1 dram), introduced and the duodenal tube removed. The tapeworm is expelled entire in ½ to 2 hours. H. Schneider (Wien. klin. Woch., Apr. 3, 1924).

When the parasite is passed, search for the head should be made in a shallow receptacle, using the microscope to identify it.

The following plan, originally described by the late Dr. Leslie Ogilvie, was found to answer in every case in which the writer tried it: For three days previous to the administration of the male fern the patient is kept entirely on a liquid diet; a pint and a half of milk and a like quantity of beef tea answer very well. To promote a free bowel action and removal of mucus, the following is given:—

℞ *Sodii bicarbo-*  
*natis* ..... gr. xx (1.3 Gm.).  
*Sodii sulphatis* ... ʒj (4 Gm.).  
*Spiritus chloro-*  
*formi* ..... ℥xx (1.25 c.c.).  
*Aq. menthae pip-*  
*erita* .. q. s. ad ʒj (30 c.c.).

Take three times a day.

On the night before the male fern is given the patient should have the following draught:—



℞ *Magnesii sulphatis* ..... ʒss (15 Gm.).  
*Tinct. jalapæ* .... fʒj (4 c.c.).  
*Tinct. chloroformi comp.* ... ℥xx (1.25 c.c.).  
*Aquæ* .....q.s. ad fʒjss (45 c.c.).

This is repeated next morning at 7 o'clock if the previous dose has not operated. A 8 A.M. male fern is given in a mixture:—

℞ *Extracti filicis fluidi* ..... fʒj (4 c.c.).  
*Pulv. tragacanth. comp.* ..... gr. xx (1.3 Gm.).  
*Spiritus chloroformi* ..... ℥x (0.6 c.c.).  
*Aq. menthæ pip-eritæ* .....q.s. ad fʒj (30 c.c.).

At 9 A.M. this dose should be repeated. At 11 A.M. a purgative is given, and if the bowels do not act promptly an enema of a pint and a half or 2 pints of soapy water administered. The movements should be carefully examined to find the head, and if the above treatment has been faithfully carried out it may be sought for with confidence. It is desirable to keep the patient in bed for two or three hours after the bowels have acted, as the male fern may cause faintness. F. de H. Hall (Clinical Journal, Aug. 6, 1908).

When capsules or pills cannot be used, the oleoresin may be given in the following way:—

℞ *Oleoresinæ aspidii*,  
*Tinct. vanillæ* ...āā ℥xxx (1.8 c.c.).  
*Pulv. acaciæ* .... ʒss (2 Gm.).  
*Aq. destill.* ..... fʒj (30 c.c.).

This is taken in one dose, the directions given above as to preparation and subsequent purgation being carefully followed.

As a remedy in **hookworm infection**, aspidium has frequently been used. Bruns treated 21,612 cases with it and found that it expelled all the parasites in 98.5 per cent. of cases, though in 15 to 30 per cent. it

was necessary to give a second dose and 4 cases of blindness occurred in the series. Ashford and King in Porto Rico found that in a certain proportion of cases ethereal extract of male fern could be used successfully where thymol had failed. The drug seemed to vary considerably in activity, however, and, because of the large doses necessary, greater nausea, dizziness, and prostration were complained of by the patients than followed the use of thymol. The dose of the oleoresin required in hookworm disease is 75 to 150 grains (5 to 10 Gm.), given in 2 doses one hour apart (Dock and Bass).

C. E. DE M. SAJOURS

AND

L. T. DE M. SAJOURS,  
 Philadelphia.

**ASPIDOSPERMA.** See QUEBRACHO.

**ASPIRATION.** See PARACENTESIS.

**ASPIRIN, or ACETYLSALICYLIC ACID**, is the acetyl derivative of salicylic acid [ $\text{CH}_3\text{COO.C}_6\text{H}_4\text{COOH}$ ]. It occurs in the form of small, colorless crystals or a white powder. It is soluble in about 300 parts of water, and readily in alcohol and ether. It is official as *Acidum acetylsalicylicum*.

**DOSE AND MODES OF ADMINISTRATION.**—The dose of acetylsalicylic acid is from 5 to 15 grains (0.33 to 1 Gm.). It should not be administered with alkalies, as these will split up the drug into acetic acid and salicylic acid, and induce the gastric discomfort which the latter acid causes in its pure state. It may be given in capsules, wafers, or in a solution with sugar or syrup and

water, but the most prompt action is obtained by placing the powder upon the tongue and washing it down with a little water, or by giving it in gelatin capsules.

Decomposition of a mixture of quinine sulphate and aspirin sometimes takes place and a poisonous product is formed, to which the term quinotoxin has been applied. Scoville (Jour. Amer. Pharm. Assoc., May, 1915).

### PHYSIOLOGICAL ACTION.—

The physiological action of acetylsalicylic acid in general resembles that of salicylic acid (*q.v.*). It was formerly asserted that acetylsalicylic acid passed through the stomach unchanged, salicylic acid not being split off from it until it reached the alkaline media of the intestine. This view, however, proved to be incorrect, the experiments of Hanzlik and Prescho having demonstrated that salicylic acid can be set free from it by the gastric juice. This is in harmony with clinical experience to the effect that the drug has a distinctly irritating effect on the stomach in some patients, and disposes of the assertion that the drug is free of the gastric irritation of the salicylates because it is not decomposed therein. Further, the investigation by Hanzlik and Prescho seemed to show that acetylsalicylic acid is only partially broken up before it is absorbed into the system, since from 8.8 to 36.6 per cent. of the amount of it administered was found to be excreted unchanged in the urine.

Many cases were encountered during the influenza epidemic in which severe stomach disturbances followed the use of acetylsalicylic acid, sometimes with actual hematemesis. The drug was taken in the usual doses and intervals, and the disturbances began

gradually and grew constantly worse, with sometimes sudden hematemesis; or melena might be the first indication of the gastric hemorrhage. Luis y Yagüe (Arch. Españ. de Enf. del Ap. Digest., Nov., 1918).

The decomposition of acetylsalicylic acid into salicylic acid at 38° C. was found by the writers to be equally marked with an acid reaction ( $pH$  5) corresponding to that of gastric juice and with an alkaline reaction ( $pH$  8 to  $pH$  9) found in the intestinal juice. The decomposition was very much less, however, in the vicinity of neutrality or very slight alkalinity corresponding to that of the blood ( $pH$  6 to  $pH$  7.4). The maximum liberation of salicylic acid *in vitro* at either acid or alkaline reaction was 4 to 5 per cent., occurring at the end of 1 hour. From 33 to 45 per cent. liberation with an acid or alkaline reaction occurred at the end of 18 hours, and there was almost complete decomposition (95 per cent.) at the end of 24 hours. On the other hand, in buffers of  $pH$  6.8 to 7.0, 98 to 99 per cent. of the drug remained unchanged at the end of 1 hour, about 95 per cent. after 18 hours, and about 45 per cent. after 24 hours.

Applying these findings to what happens to the drug in the human body, the maximum decomposition of it would be expected to occur in the stomach. At the end of 1 hour, while absorption of the drug is proceeding, about 95 per cent. of it would exist in the form of the undecomposed sodium salt—sodium acetylsalicylate. This salt would therefore be present in the circulation, since the blood reaction ( $pH$  7.4) does not favor decomposition of acetylsalicylates. A considerable absorption and urinary excretion of the unchanged acetylsalicylic group would therefore be expected. That this actually occurs was shown by giving the drug to 6 patients, comprising 4 convalescents and 2 suffering from rheumatic fever. The total excretion after administration of 4 to 14.8 Gm. (clinical toxic doses) was from 8.8 to 36.6 per cent. The excre-

tion bore no relation to clinical condition, dosage, diuresis, total salicyl excreted or other factors. The duration of excretion was 3 to 6 days. The proportion of acetylsalicylic acid in the total salicyl extracted ranged from 5.3 to 41.1 per cent. P. J. Hanzlik and E. Presko (Jour. of Pharm. and Exp. Ther., May, 1923).

Acetylsalicylic acid has been credited with a less tendency to produce depressing effects on the heart as compared to the salicylates. According to the experiments of Mendenhall and Camp, indeed, the drug has a direct stimulant effect on the heart. The drug does not seem to cause tinnitus as readily as the salicylates. According to some, it has a contracting action on smooth muscle, including that of the uterus.

From experiments on the frog's heart, *in situ* or isolated, as well as blood-pressure studies in cats, the authors maintain that acetylsalicylic acid is not depressant to the heart or circulation in ordinary nor in very large doses, but instead has a direct stimulant effect on the heart-muscle. In the cat experiments, in which the drug was injected intravenously in doses comparable to or larger than those used in man, an increased heart-rate and blood-pressure uniformly followed. This observation accounts for the rarity of reported fatalities from this widely used drug. The occasional strong or unusual heart beats in patients taking acetylsalicylic acid may be due to the increased irritability of the heart-muscle induced by the drug. W. L. Mendenhall and H. F. Camp (Boston Med. and Surg. Jour., Feb. 21, 1924).

**ACETYLSALICYLIC ACID POISONING.**—The most evident toxic effect, either in an oversensitive subject or after large doses, is edema of the face, especially about the eyes, nose, and mouth. The pharynx and larynx may also be involved, expos-

ing the patient to death from edematous laryngitis. The lips and eyelids are usually congested and everted, and there may be severe headache and tinnitus. There may be great dyspnea, difficulty of deglutition, and marked rapidity of the pulse, with cyanosis involving the entire body. An eruption, urticarial or erythematous, may appear after these symptoms or appear alone, as in a case witnessed by Elverson.

Case in which  $7\frac{1}{2}$  grains (0.5 Gm.) of aspirin, every thirty minutes, eight times, caused considerable general cyanosis, with cold extremities. The heart's action was 70 and very weak, intermitting every third or fourth beat. The skin was rather harsh and dry. The mind was perfectly clear. There was some nausea, with vomiting at intervals. The writer removed the stomach contents at once by means of **stomach-tube**; the stomach washings consisted merely of some mucus and biliary coloring matter. He applied **external heat** to the back and extremities, and gave **strychnine**, gr.  $\frac{1}{30}$  (0.0022 Gm.) hypodermically. The patient began to rally after two hours, and recovered. Cooper (W. Va. Med. Jour., June, 1910).

The writer observed a patient who, after taking a capsule containing 5 grains (0.5 Gm.) of aspirin was taken with vomiting in about half an hour, followed by a "stiffness" in the throat making him think he was developing a tonsillitis. An hour and a half after taking the capsule his face was swollen and cyanotic, the eyelids were edematous and almost closed and the conjunctiva injected, the whole face swollen, the breathing was labored and asthmatic, the nasal mucosa gorged, preventing nasal breathing, the buccal mucosa and pharynx were dark red and swollen, the uvula twice its normal size. The pulse was 120, soft and full, temperature 98. The breathing was such as one might expect with edema of the glottis. No

treatment was instituted; the symptoms largely disappeared in 6 hours, but there was a fine, papular rash on the trunk the next morning. The patient reported a similar experience about a year before, lasting about 5 hours, after taking a capsule of  $2\frac{1}{2}$  grains (0.16 Gm.) each of aspirin and phenacetin. E. N. Reed (Jour. Amer. Med. Assoc., Mar. 7, 1914).

The writer mentions 17 cases from the literature, and reports 3 seen personally, in which the use of acetylsalicylic acid was followed by edema, the lids and face swelling, the skin puffing up sometimes down as far as the chest. In some of the cases there was also a tendency to urticaria, near the swollen patches or more diffuse. In some of the cases the edema involved the mucosa of the nose and pharynx; in 2 cases there was edema of the larynx. The edema rapidly reached its height and subsided as a rule in 24 hours.

The doses administered had ranged from 0.3 to 1 Gm. (5 to 15 grains), and the pathologic reaction occurred always at the first dose, independent of the amount taken. In 2 of the cases the drug was continued without further mishap. A. Klercker (Hygiea, lxxviii, No. 4, 1916).

A case of chronic aspirinism was observed by the writer in a woman, aged 50, suffering from rheumatoid arthritis. She took 10 grains (0.6 Gm.) of aspirin twice daily for 7 years. During the first 6 years of the treatment she exhibited no sign of poisoning, nor of gastrointestinal irritation nor of cardiac or mental depression. The first untoward sign was an intractable simple conjunctivitis, the patient complaining of "sand in the eyes." There was a well marked hyperemia of both the palpebral and ocular conjunctiva; there was a slight degree of chemosis and considerable lachrimation. A week later an urticaria appeared which was not relieved by either dietetic or the usual local or internal remedies. In a few days the patient was entirely covered by a typical urticaria major,

the rash, assuming in parts the character of an acute circumscribed edema, and elsewhere a severe urticaria bullosa. The patient was weak from insomnia, had diarrhea and vomiting. Massive edema of the tongue and fauces, causing marked dysphagia, an urgent tracheotomy being only averted by a prolonged administration of ice and ice water combined with astringent gargles. Vision was obstructed by an extreme palpebral edema. The urine gave an intense bluish violet reaction when tested with liquor ferri perchloridi, but the exact percentage of salicylic acid was not estimated. A diagnosis of chronic aspirinism was made, and the drug rigidly withheld.

Medicinal treatment consisted of 5 grains (0.3 Gm.) of *ichthyol* and a mixture containing *liquor arsenicalis*, *tincture of belladonna* and *calcium lactate*, 3 times a day. **Bromides** were administered in large doses every night. At the end of the seventh week all trace of the urticaria had vanished and the urine was again normal. Moreover, since the onset of the urticaria, although all aspirin had been discontinued, all traces of the rheumatism beyond the bony deformities, had disappeared. W. F. Stiell (Pract., Sept., 1917).

Case of a man who had a chronic periostitis and osteitis of one tibia who, having found that a tablet of aspirin, 5 grains (0.3 Gm.), gave him distinct relief, continued to take the drug. At first one or two 5-grain (0.3 Gm.) tablets sufficed to keep him comfortable one whole day, but soon the patient had to increase the dose. For the past 2 years he has been taking from 5 to 12 tablets of the drug daily. The only abnormal features were obstinate constipation, slight digestive disturbances, and a rather low blood-pressure. Macht (Med. Rec., Nov. 2, 1918).

Case of aspirin addiction in a man aged 21, who had begun to use the drug for pain from abscessed cervical glands. Starting with 15 to 20 grains (1 to 1.3 Gm.) daily, he gradually in-

creased the dosage until he was taking 305 grains (20 Gm.) a week. This amount failed to give relief. Emotional irritability when attempts were made to withdraw the drug required his commitment to a state insane hospital. He was extremely weak, with feeble heart sounds, irregular pulse, dyspnea, passive congestion at both bases, epistaxis and hemoptysis. Hearing was impaired and tinnitus complained of. In 48 hours after admission the temperature rose to 103° F. and showed a septic curve. The tissues of the neck were swollen and hard, but the general condition precluded operation. Aspirin was at once withdrawn, general supportive treatment begun, and the pain controlled for the first 2 weeks by morphine sulphate,  $\frac{1}{6}$  grain (0.01 Gm.) once or twice a day. He gradually improved, but the hearing remained impaired and he still craved aspirin. J. A. Jackson and H. V. Pike (Ther. Gaz., Oct., 1922).

### TREATMENT OF ACETYLSALICYLIC ACID POISONING.

—Withdrawal of the drug is, as a rule, followed by gradual convalescence. As the morbid condition is probably due to arterial spasm, **hypodermoclysis**, to fill out the vessels, dilute the drug, and promote diuresis, is indicated. A purgative should be given to insure the evacuation of what the intestine may contain. Threatening edema of the larynx demands **scarification** of this organ followed by the **local application** of 1:5000 **adrenalin** solution.

As shown above, the toxic phenomena provoked by aspirin differ markedly from those caused by the ordinary salicylates or even salicylic acid. The fact referred to by Chidichimo, that the drug causes contraction of smooth muscle-fibers, suggests that **amyl nitrite** inhalations, **nitroglycerin** injections, or in mild

cases **sweet spirit of niter**, should be tried. **Heat** to the surface is a valuable adjunct. **Strychnine** hypodermically is indicated when there is prostration.

**THERAPEUTICS.**—Acetylsalicylic acid may be employed in **rheumatism** in its various forms, **articular** and **muscular**, and even in “**growing pains**.” Given in 10- to 15-grain (0.66 to 1 Gm.) doses every four hours, the temperature, if high, usually falls to normal about the third day, when the dose may be gradually reduced until 5 grains (0.33 Gm.) are given at the same intervals. This should be persisted in three or four weeks; otherwise a relapse is apt to occur. Its efficiency is quite as marked in children, in doses adjusted to the age. Acetylsalicylic acid seems to possess greater antipyretic power than any of the salicylates, even 4-grain (0.25 Gm.) doses exerting such an effect in **typhoid fever** (Bondi).

The writer has given aspirin in 15-grain (1 Gm.) doses in **neuralgic affections**, especially those of the jaw. Usually in a half-hour the pain is lessened, and in an hour entirely disappears. In severe **sciatica** it has proved very efficient, being given in the same dose in connection with a saline cathartic. The pain returned at the end of twelve hours, but with lessened intensity. F. Tribold (Wien. klin. Rundschau, Sept. 9, 1900).

The writer has prescribed this drug over a thousand times for various ills, more especially all kinds of acute and chronic **rheumatic ailments**.

While some writers on aspirin have recorded peculiar forms of intoxication, as well as exanthemata, due to aspirin, the writer has not as yet met any such unpleasant symptoms. This is possibly due to the fact that in patients whose vascular system appeared weak he always added to each

dose 0.1 Gm. ( $1\frac{1}{2}$  grains) of powdered ergot. These good results were not obtained by avoiding large doses; on the contrary, the writer prescribes this drug in 1-Gm. (15 grain) doses, to be taken every second or third hour, as deemed necessary. E. Klaveness (St. Paul Med. Jour., Aug., 1910).

The writer gives patients suffering with **typhoid** of moderate severity 3 grains (0.2 Gm.) of aspirin as an antipyretic, repeated every four hours; where there is little sign of action the dose is increased to 4 or 5 grains (0.26 to 0.32 Gm.). It should never be administered in tablet form, but dissolved in water containing a little sodium bicarbonate, which increases its solubility. Chambers (Brit. Med. Jour., Jan. 20, 1912).

Study of the effects of acetylsalicylic acid during febrile and afebrile phases, as well as in the first stages of convalescence. The phenomena were similar in both stages. In 1 Gm. (15 grain) doses it exhibited a marked antipyretic effect in all. In  $1\frac{1}{2}$  hours the temperature change averaged  $0.81^{\circ}$  C. in 6 experiments on 4 persons, in contrast to an average rise of  $0.18^{\circ}$  C. on 4 control days. In the control experiments the heat elimination averaged 37.7 calories per square meter per hour. When the drug was given it became 52.1 calories, an increase of 38.2 per cent. The antipyretic effect was due essentially to this change, which was associated with marked perspiration and subjective warmth. The fall in temperature was accompanied by a heat production of 38.8 calories per square meter per hour, a decrease of 3.5 per cent. below the 40.2 calories of the control days. This change was due probably to the cooling of the body. Barbour (Arch. of Int. Med., xxiv, 624, 1919).

Some authors claim equal merits for it in the treatment of **acute gout**; it is certainly of value in the **migraine** which frequently attends the gouty diathesis, **sciatica**, **neuralgia**, and most varieties of **headache**.

It has been found very efficient in **chorea** and will sometimes abort an attack of **acute coryza**, even the form which frequently initiates **influenza**, and is useful in **cough**.

The writer has had good effects in **cough** with aspirin, even when codeine had failed. It tends to shorten the duration of the cough. Ebstein (Deut. med. Woch., xxxvii, 1476, 1911).

Acetylsalicylic acid has also been used with success in **dysmenorrhea**, especially when morphine is for any reason contraindicated, as well as to control bleeding in **metrorrhagia** and **labor pains**.

In **labor** aspirin relieves pain without diminishing uterine contraction. In 276 gynecological cases the writer obtained the best results in **inoperable carcinoma**, **dysmenorrhea**, and disease of adnexa; also using aspirin as a means of relief in **painful uterine contraction** after operation. He gives 7 grains (0.45 Gm.) every half-hour up to 4 doses; 15 grains (1 Gm.) are given at a dose in cancer cases. Unpleasant symptoms were observed if upward of 45 grains (3 Gm.) were given. Goth (Gyegyaozat; Zentralbl. f. Gynäk., Nu. 38, 1904).

Aspirin acts well in ovarian **dysmenorrhea**, as it not only diminishes the general nervousness, but also lessens the ovarian hyperesthesia. In uterine dysmenorrhea, with functional nervous disorders which have no organic basis, it acts as a strong analgesic. In severe diseases of the adnexa and **chronic metritis**, the drug lessens the intensity of the dysmenorrhea. If one administers aspirin shortly before menstruation the dysmenorrhea will be suppressed. Aspirin has a beneficial influence upon **amenorrhea** and **menorrhagia**. The drug produces diminution of pain in the genital apparatus, whatever be its cause. The usual dosage is 10 to 15 grains (0.65 to 1 Gm.) two or three times daily. F. Chidichimo (Therap. Monats., Nu. 8, S. 389, 1906).

In **asthma** of the bronchial type, aspirin has been found to lessen the violence of the attack and to curtail its duration. It is said to relieve the fulgurant pains of **tabes dorsalis** and the gnawing pains of **gastric cancer** and of **inoperable cancer** elsewhere.

The writer found aspirin useful in the management of **inoperable carcinoma**; 7 to 15 grains (0.45 to 1 Gm.) relieve the pain in severe cases, and often permit sleep. In some cases morphine was not well borne; aspirin was quite as effective. Ruhemann (*Deut. med. Woch.*, June 2, 1904).

In **acute pharyngitis** or **tonsillitis** the writer recommends 1 to 3 grains (0.06 to 0.2 Gm.) of acetylsalicylic acid, taken on the tongue without water every 3 or 4 hours. In 1000 cases of **tonsillectomy** the measure likewise proved of marked value in relieving the local discomfort during convalescence. Most patients were enabled to swallow without pain at once. The use of the drug was begun about 8 or 10 hours after the operation and continued thereafter, 10 or 15 minutes before every meal, for 3 or 4 days. The action is believed to be exerted locally. Where an idiosyncrasy is known to exist, a solution of 5 grains (0.3 Gm.) in 1 ounce (30 c.c.) of water may be used as a gargle, and will yield almost equivalent results. E. P. Heller (*Ther. Gaz.*, Dec., 1921).

Acetylsalicylic acid should be avoided where there is cardiac weakness, or where, in acute disorders such as influenza or scarlatina, the stage of depression has been reached. It has been recommended in acute infections, but the possibility of its depressing the heart imposes a certain amount of caution in its use in such cases.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

## ASTEATOSIS, or XEROSIS.

—This is a disorder of the skin characterized by abnormal dryness, which, if the condition be at all severe, is accompanied by desquamation, induration, cracking, and sometimes thickening. It is due to scantiness or absence of the sebaceous secretion, and sometimes also of sweat. It may be caused by the action of substances, such as strong alkaline fluids, which absorb these secretory products from the cutaneous tissues, or may occur in association with or as a sequel of certain skin affections, such as ichthyosis, eczema, exfoliative dermatitis, etc. It is often met with in aged subjects owing to the deficient activity of all functions, including those of the skin, and is always observed in cases of true cretinism or myxedema owing to the existence of deficient metabolism in and nutrition of the skin, including its glandular elements.

**TREATMENT.**—The treatment of asteatosis resolves itself into the elimination of the cause and the application to the skin of oleaginous substances, **vaselin**, **cold cream**, etc., at regular intervals.

In cases of myxedema or cretinism, the usual treatment: **thyroid gland** in 1 to 3 grains (0.065 Gm. to 0.19 Gm.), doses according to the age, three times daily, benefits the asteatosis along with the malady itself. Thyroid in small doses (1 gr.—0.065 Gm.) night and morning might also be tried in senile asteatosis where the subject does not show evidences of arteriosclerosis. S.

**ASTHMA.—DEFINITION.**—A disorder characterized by more or less severe paroxysmal dyspnea, due to spasmodic narrowing of the bronchial lumen, frequently with hyperemia of the bronchial mucosa.

**SYMPTOMS.**—In what has been termed "true asthma," *i.e.*, the typical form of this disease, premonitory symptoms—such as uneasiness about the chest, pallor, or a feeling of exultation, due to unusual good health—occasionally warn the patient that an attack is impending. A dyspneic

laugh, repeated sneezing, stridulous laryngitis, dyspepsia, and copious urination have been observed as prodromata of a paroxysm. Or, it may be preceded by depressive mental states, moroseness, irritability, drowsiness, headache, and vertigo.

Suddenly, in the early hours of the morning in the vast majority of cases that occur in adults—children not being as markedly prone to this nocturnal type—great constriction of the chest and more or less marked suffocation, referred to the sternal region, are experienced.

The dyspnea, in bad cases, almost reaches the stage of apnea; the respiration is wheezing in the milder cases, but in the others it is scarcely audible. The suffering of such cases is intense; the patient assumes various positions calculated to assist respiration; there is prominence of the eyeballs, distention of the superficial vessels of the neck, blueness of the lips; the skin is clammy and covered with sweat, etc.

Differentiation of the various forms of asthma may be made according to Minervini, by the attitude of the patient during the attack. In *bronchial* asthma the patient rises to reach the window for air, retaining his sense of direction and co-ordination. If he can seize the back of a chair with both hands he clings to it, his shoulders raised and his body stooping forward. In *cardiac* asthma the patient is much weaker during an attack. He sinks into a chair or sits on the side of his bed, immovable, dumb, anxious, supporting himself with his hands on the seat of the chair or bed beside him. In *uremic* asthma the patient also assumes this position from lack of energy to rise, but he is much agitated and tosses his arms and legs about, the convulsive agitation sometimes passing into a rapidly fatal depression.

The number of respirations per minute is usually reduced and the

expirations are very much prolonged. The chest remains expanded, barrel-shaped, owing to the patient's inability to contract it and expel the air; the abdomen is inordinately protruded through the descent of the diaphragm, and its muscles are tense and hard. Percussion gives rise to a drum-like, somewhat high-pitched note over the areas of the chest in which the distention of the alveoli by the imprisoned air is most marked. The cardiac and hepatic dullness outline becomes narrow and occasionally suppressed by the overlying inflated lung.

Auscultation reveals sibilous rhonchi of varying pitch and intensity, following the rhythm of the respiration. They resemble the chirping of birds of different varieties and size, simultaneously heard. This is accompanied or followed by mucous râles.

The variations in the pitch of the notes heard are due to the variations in the diameter of lumina left in the bronchi. Mucous râles are present, absent, coarse, or fine according to the nature of the secretions present. Sometimes nothing but the sibilous rhonchi are heard.

The pulse is usually slow and weak and the temperature is normal in the majority of cases, rarely reaching 100° F. Frequently it descends to 97½° F.

After a period varying from half an hour to several hours the symptoms abate and end by a more or less profuse expectoration of viscid, stringy mucus, varying in opacity according to the severity of the attack.

In a small proportion of cases the fever, cough, and purulent nature of



the sputum tend to show that catarrhal bronchitis is present as a complication. It is in these cases that emphysema is most likely to occur later on. Pulmonary tuberculosis may also occur concomitantly with bronchial asthma; the latter may subside as the former becomes installed (Hedenius).

The writer holds that asthma is not always a diffuse process but often limited to a small area in one lung. Although the signs may be localized the symptoms may be localized or general. Whether primarily or secondarily infected the first evidence of pulmonary tuberculosis is an enlargement of the bronchial glands. Their enlargement is a part of the normal mechanism for the battle against the disease. It is through their functioning that antibodies are manufactured. When the subject is enjoying good health the glands are not interpreted as a tubercular focus; it is only when he is below normal that they are considered as a source of potential or possibly actual danger. P. H. Pierson (Calif. State Jour. of Med., June, 1918).

The expectorated substance is found to contain minute angular, octahedral crystals, visible with medium-power lenses, and recognized as the Charcot-Leyden crystals. They are soluble in warm water, the alkalis, and the mineral acids. These properties, as shown by Salkowski, are those of mucin. The association is further supported by the fact that Loewy found the same crystals in the gelatinous nasal polypus, although asthma was not present.

The Charcot-Leyden crystals of the ordinary shape are composed of secondary calcium phosphate. In the less usual crystals of rhombohedral shape there is present in addition some calcium carbonate. Van Leeuwen and Nijk (Klin. Woch., July 2, 1923).

The sputum also contains Curschmann's spirals, which are frequently sufficiently large to be recognized with the naked eye. They consist of a fine, closely packed layer of epithelial cells arranged in a spiral form around a longitudinal canal-like film. They are usually found in the thickest portions of the sputum. These are not pathognomonic of asthma, being also found in the diseases characterized by exudative inflammation of the bronchioles, as shown by Vierordt.

Large lymphoid bodies and granules, the eosinophile cells of Ehrlich, are also found, the latter sometimes in sufficient quantities to constitute a true eosinophilia.

In 150 cases studied, 123 differential blood smears showed a relatively constant eosinophilia averaging about 5 per cent., but there has appeared no significant difference between the eosinophilia in cases of extrinsic from that in cases of intrinsic asthma, nor any significant difference in the counts made during and between the asthmatic attacks in either divisions. Rackemann (Boston Med. and Surg. Jour., June 6, 1918).

Stress laid on the differential importance of eosinophilia in the sputum. The absence of eosinophilia in other cases of dyspnea excludes the assumed asthma, and directs elsewhere the search for the cause of the disturbance. This is particularly important in men over 50 with attacks of distress in breathing at night. The eosinophiles are readily shown up by staining with hematoxylin-eosin after fixation with alcohol-ether or methyl alcohol. Benzançon and de Jong (Bull. de l'Acad. de méd., Nov. 30, 1920).

In a study of 96 cases of primary and 11 of secondary asthma, and of 7 of hay-fever, *leukopenia* as an index of hemoclasia was found in 77 per cent. In most cases the leukocytes decrease and then increase regularly. In a

smaller number these variations are irregular; or are preceded by or alternate with a slight hyperleukocytosis. Galup (Presse méd., Feb. 1, 1922).

The urine is generally very copious, of low specific gravity, and light colored. It is usually more toxic after a night attack.

Occult gastrointestinal bleeding is sometimes an accompaniment of asthmatic attacks. According to Manwaring and his co-workers, increased capillary permeability is an important physiologic change in protein sensitization. Out of 44 cases in which the stomach contents were examined 18 showed blood, while out of 25 examinations of feces 10 were positive. Gastrointestinal disturbance being a frequent symptom of human allergy, it is well to remember that blood in the stomach contents or feces does not necessarily imply the existence of an organic lesion, such as ulcer. W. Lintz (Boston Med. and Surg. Jour., June 5, 1924).

The most important complication of asthma is emphysema. This is due to the repeated narrowing of the bronchi, which, assisted by the resulting local congestion, becomes more or less permanent and causes dilatation of the alveoli.

The pulmonary circulation is interfered with, and dilatation of the heart and edema may occur. The conformation of the patient's frame becomes changed, owing to modified action of the muscles of the back and chest. The sufferer stoops and his shoulders become raised.

In late years a large proportion of cases have been attributed to allergic sensitization to one of many substances, protein, pollen, etc. In these cases alternating attacks of urticaria and asthma are sometimes observed. (For further details see the section on Etiology.)

The close relationship of Besnier's *diathetic prurigo* to the anaphylactic state existing in many cases of asthma is emphasized by the writer. This skin condition is characterized by severe itching on the flexor surfaces of the joints. The writer found it 13 times among 67 cases of asthma below 20 years of age, usually with a history of recurrent eczema of the face, scalp and other areas in the first few months of life, followed at 1 to 7 years by restriction to the flexor surfaces of the elbows and knees. This condition either accompanied attacks of asthma or followed the taking of certain foods. Every case tested was found hypersensitive to pollen, feathers, horse dandruff, egg or other allergens. K. Baagöe (Ugeskr. f. Laeger, Aug. 14, 1924).

**DIAGNOSIS.**—**Laryngeal and Tracheal Disorders.**—Attacks resembling those of the typical form may be induced by pressure on the trachea, aneurisms, goiter ("thymic asthma"), foreign bodies, vertebral disease, glandular enlargement, growths of the larynx and of the infraglottic space.

In 2 of the writer's 4 cases of tracheal tumor, the condition was at first mistaken for asthma. There were 2 cases of endothelioma and 1 case each of sarcoma and fibroma of the trachea. Adam (Jour. of Laryng. and Otol., Mar., 1926).

As the writer showed in 1895, infraglottic disorders, growths, and syphilis especially may give rise to a form of dyspnea simulating that of asthma. Macintyre has also noticed that the great majority of urgent cases of acute stenosis can be seen low down in the larynx, either in the region of true or false vocal cords or below the glottis.

In croup and other laryngeal diseases there is also interference with the respiration, but it is with the inspiration and not with expiration.

**Bronchitis.**—In children asthma sometimes assumes the character of capillary bronchitis. In all forms of bronchitis there are absence of periodicity, greater amount of expectoration, marked increase in number of respirations, free chest motion, and more or less fever.

**Pneumonia.**—In this disease the respirations are greatly increased in number, and there is panting, besides free chest motion. There is also high fever.

**Emphysema.**—In emphysema the dyspnea is continuous, though liable to exacerbations. The dyspnea of emphysema is often attributed to asthma. While, according to Schech, bronchial asthma of nasal origin occurs when the patient is at rest, and especially at night, the dyspnea of emphysema mostly appears on exertion.

**Guha.**—This epidemic disease, noted and described by our naval surgeons in Guam, has many of the symptoms of bronchial asthma. It attacks chiefly children and infants, there is marked fever, and it assumes more the character of bronchial catarrh.

Guha, which simulates asthma, is, according to McCullough, characterized by hemorrhagic infarction of the lungs, intestinal ulceration, cloudy swelling of the parenchymatous organs, and enlargements of the mesenteric and mediastinal lymph-nodes. The initial symptoms occur either in the lungs (pneumonic type) or intestinal tract (enteric type). In the primarily pneumonic type the enteric symptoms never become the more prominent, and *vice versa*. The course of the pneumonic type is sharply defined from bronchial asthma in the following respects: 1. The number of respirations is considerably increased. 2. There is continued fever. 3. The amount of expansion is not so disproportionate to the respiratory movements.

4. Inspiration is not so short and quick, and expiration is not so prolonged. 5. The percussion note has not the same hyper-resonant quality. 6. Paroxysms subside gradually, never suddenly.

**Heart Disease.**—Dyspnea usually follows exercise or becomes greatly aggravated by it in cardiac disorders. In advanced cases the dyspnea is continuous and the cardiac lesions are easily recognized. As Merklen observed, cardiac asthma occurs suddenly at night, on account of the greater tendency to venous stasis, with dyspnea lasting at most a half-hour. The attacks generally reappear night after night, rarely twice in one night. They occur in cases of mitral insufficiency with loss of compensation, and in cases of advanced arteriosclerosis with cardiac dilatation, myocarditis, and renal insufficiency.

A group of cases presenting asthmatic symptoms on account of myocardial insufficiency, independently of the so-called "cardiac asthma" manifested in nocturnal paroxysmal dyspnea, is recognized by the writer. The etiology is essentially that of chronic myocarditis with decompensation. These patients are not suffering from sensitization and are beyond middle life. Too often such cases are given no relief from their asthma on account of failure to appreciate the incipient cardiac impairment. The treatment consists of diet, rest and digitalis. The latter is effective even when the heart beat is regular. Epinephrin does not relieve the asthmatic symptoms in these cases, and is even contraindicated. M. M. Peshkin (Med. Jour. and Rec., May 21, 1924).

**Spasm of the Diaphragm.**—In this symptom there are sudden spasmodic expulsive efforts, frequently accompanied by hiccough.

**Renal Disease and Uremia.**—The presence of renal disease may be de-

terminated by examination of the urine, which should always be practised whenever dyspnea occurs as a prominent symptom. The dyspnea occurring as a symptom of uremia is more or less continuous and accompanied by presence of casts in the urine.

Kelp has reported a case in which attacks of asthma alternated with hallucinations, weakness of will and intelligence, followed by depression, distress and ideas of being poisoned. As the mental condition returned to normal, the asthma recurred. Norman has also reported 7 cases in which a tendency to asthma coexisted or alternated with periods of mental impairment. In only 1 of the 7 the asthma persisted unmodified during the intercurrent psychosis, an acute melancholia.

In the case of a young man personally observed by the writer, the asthma seemed to be mitigated during the periods of the psychosis, but never entirely. Houckgeest (*Nederlandsch Tijdsch. v. Geneeskunde*, May 11, 1918).

**ETIOLOGY AND PATHOLOGY.**—Heredity shows itself in about one-half of the cases when three generations are included in the computation. If diathetic diseases such as rheumatism, gout, migraine, etc., are included as predisposing factors, as taught by Trousseau, almost every case will be found to be hereditary.

In a series of cases of bronchial asthma comprising 77 in patients under 10 years of age and 33 in patients between the ages of 10 and 20, 19.1 per cent. gave a history of allergy on both sides of the family and 51.8 per cent. a unilateral family history of allergy. Rowe (*Amer. Jour. Dis. of Childr.*, Jan., 1926).

Asthma presents itself before the age of 10 years in one-fourth of the

cases, but it may occur at any period. It is more frequent among males than among females. The wealthy are more prone to it than the poor, and there is a predilection for persons deprived of physical exercise, such as clergymen, lawyers, clerks, etc. Auto-intoxication of intestinal origin, often due to sedentary habits, and termed "stercoremia" seems a predisposing factor.

Atmospheric influences are active factors in the production of an attack. Excessive dryness, such as that of overheated or insufficiently ventilated rooms, or, on the contrary, excessive dampness, may bring on a paroxysm. Cases in which gout, rheumatism, etc., exist are especially sensitive to dampness.

Asthma sometimes appears during pregnancy. If the patient has previously suffered from bronchial asthma, the paroxysms of the latter may increase in intensity during gestation. The fact that the thyroid is enlarged during pregnancy is interesting, especially in view of the occasional presence of asthma in goitrous cases even though no pressure is exerted by the tumor upon the trachea.

Various theories have been propounded to explain the dyspnea, but the prevailing one today is that it is due primarily to spasm of the smaller bronchi, as taught by Laennec, Biermer, and Williams. With this may occur, secondarily, a spasm of the muscles of the thorax and of the diaphragm, which are unable to cause expulsion of the air imprisoned in the alveoli on account of the restricted lumen of the bronchi.

From experiments on excised human and animal lungs and on living human

subjects the writer believes there can be no doubt that, when the bronchioles are contracted in asthma, the dilatation of the lungs is a necessary process helping to keep the bronchioles sufficiently open to allow the passage of the minimum air requirement. To be able to expel air at all, the lungs must be widely distended. Constant inspiratory effort is exhausting, however, and when the patient relaxes his respiratory muscles he again experiences difficulty in breathing. The experiments on excised lungs showed that the lumen of the bronchioles increases considerably when the surface of the lung is under an appreciable negative pressure. C. Sonne (*Acta med. scandinav.*, Sept. 6, 1923).

Abnormal conditions may also be present in the bronchial mucous membrane, which may be the seat of more or less catarrhal inflammation attended with swelling—an added cause of dyspnea. Some observers

Bronchial hyperemia is most apt to occur in asthma observed in the course of infections.

The *allergic origin* of asthma was brought to light by Meltzer, who suggested in 1910 that the stenosis of the bronchioles in asthma might arise in the same way as the anaphylactic bronchoconstriction observed in animals, especially guinea-pigs. The allergic nature of horse asthma was later shown by Goodale by means of skin tests, and soon after came the investigations of Talbot as to sensitization to certain foods as causes of asthma in children, and of Walker regarding bacterial proteins and various other foods. The asthma attending hay fever had already been attributed to sensitization to pollens.

The possible causes of allergic asthma have been grouped by Kolmer as follows:

- |                                       |   |   |
|---------------------------------------|---|---|
|                                       | (a) Pollens—hay fever.  | 1. Dandruff and hair of horse, cat, dog, etc. |
| I. <i>Inspiratory Type</i><br>due to: | (b) Animal emanations and dusts.  | 2. Feathers.                                  |
|                                       |   | 3. Flour dust.                                |
|                                       |   | 4. Orris root.                                |
|                                       |   | 5. Face powders, especially rice powder.      |
|                                       |   | 6. House and hay dusts.                       |
|                                       | (c) Drugs, as arsphenamin dust.   |   |
| II. <i>Alimentary Type</i><br>due to: | (a) Various meats.  |   |
|                                       | (b) Fish and shell-fish.  |   |
|                                       | (c) Milk and eggs.  |   |
|                                       | (d) Grains, as oats, wheat, rye, etc.   |   |
|                                       | (e) Vegetables, as peas, beans, potato, etc.  |   |
|                                       | (f) Fruits, as orange, banana, etc.   |   |
|                                       | (g) Nuts, as walnut, pecan, etc.  |   |
| III. <i>Bacterial Type</i><br>due to: | (h) Drugs.  |   |
|                                       | (a) Bacteria in the upper and lower respiratory tracts.                                       |   |
| IV. <i>Parenteral Type</i><br>due to: | (b) Foci of bacteria and mucoid secretions in the nose and accessory sinuses, etc.            |   |
|                                       | (a) Subcutaneous and intravenous injections of horse-, sheep-, or other alien serum or blood. |   |
|                                       | (b) Injections of drugs.  |   |

have attributed the paroxysms solely to this cause; but their sudden onset and, under proper medication, equally sudden disappearance, point clearly to the bronchial spasm as the predominating factor.

Sensitization being regarded as the most important single cause of bronchial asthma, investigation of the existence and nature of it is, as a rule, an essential procedure in the presence of this disorder. First of all, how-

ever, care should be taken to eliminate such other causes of dyspnea as cardiac or renal disease, hypertension, mediastinal tumor and advanced pneumonokoniosis. Then, to find out to what materials the patient is sensitive, a careful history and skin tests are required.

The procedure in performing skin tests for asthma is described by Talbot thus:

A linear scarification is made about  $\frac{1}{2}$  inch long, and only deep enough to penetrate the outer layers of the skin, care being taken not to draw the blood. In each case an extra scarification is made as a control, because it is a well-established fact that the mechanical injury to the skin may result in a pseudo-reaction (an elevated white area surrounded by small roseola), especially in patients with an "exudative diathesis." The scarifications are then inoculated by placing the materials to be tested (preferably in fresh solution) on the scarifications, and watching them for 20 minutes. A positive reaction appears in from 10 to 20 minutes, and in rare instances a delayed reaction is seen in 1 to 2 hours. A positive reaction gives an urticarial wheal with an irregular outline surrounded by a pink blush, both of these phenomena being absent in the control. In some cases the blush, without the urticarial wheal, is so pronounced that there is no question that there is a positive reaction. Itching may or may not be present. The reaction usually disappears within  $\frac{1}{2}$  to 2 hours. The more delicate the skin the more sensitive it is to foreign protein, and the more readily will it react when it is unbroken or only slightly broken.

Seasonal variation suggests pollen or certain foods, as strawberries. Many non-sensitive cases are also seasonal, being worse in winter or in early spring and late fall, but it is unsafe to consider a case non-sensitive merely because of such a history. Some patients sensitive to one thing or another are troubled only when their bronchial mucosa has been made abnormally permeable by infection. Attacks of house-dust or feather

asthma are generally nocturnal. House-dust cases often are troubled only in a certain house, or even in a certain room. An observed relation between a certain food and the attacks should be accepted with due caution, since it is a common observation that asthmatic attacks may follow a heavy meal. One should learn to what animal emanations the patient is exposed, and to avoid error he should be required to submit specimens. If anti-spasmodics, notably adrenalin, fail to relieve an attack, there is little likelihood of uncomplicated allergy.

Skin tests are indispensable. The practitioner should content himself with the cutaneous test. In house-dust testing the writer half fills a wide-mouthed 2-ounce bottle with the dust, adds enough 14 per cent. alcohol to make a thin mud, and allows to stand for 2 days. A drop of the supernatant fluid on a skin cut is used in the test.

Many cases that begin as a seasonal pollen asthma are prolonged into the fall and winter and finally become perennial because of complicating infection. It is, therefore, essential in diagnosis to locate all sites of infection—tonsils, sinuses, teeth, middle ear—as well as bronchial infection. R. A. Kern (Ann. of Clin. Med., Sept., 1923).

A not infrequent cause of diagnostic failure is that the test substance was improperly prepared or has deteriorated. The test products of different firms vary greatly in potency. Many of these substances can be easily prepared by extracting with 18 per cent. alcohol. Another cause of failure is performing the skin tests at the wrong time. When the skin test to a suspected substance has proven negative it should be repeated, preferably just before or during an attack. The state of the vegetative nervous system at the time is an important factor in determining an attack, in addition to the allergic substance. W. Lintz (Ann. of Clin. Med., Mar., 1924).

Out of 110 cases of bronchial asthma in children, over  $\frac{2}{3}$  of whom were below 10 years of age, 95 per cent. gave

1 or more positive skin reactions; 71.07 per cent. reacted to proteins of animal emanations. Reactions to feathers were obtained in 58.2 per cent. and pollen reactions in 40 per cent. The importance of food as a cause is emphasized by the fact that 53.6 per cent. gave such reactions. Wheat and egg proteins gave reactions in 22 and 21 per cent., respectively. Vegetables gave reactions in 31 per cent. Corresponding treatment gave complete or nearly complete relief in 68.3 per cent.; marked relief in 22.7 per cent.; slight relief in 6.3 per cent., and no relief in 2.7 per cent. Rowe (Amer. Jour. Dis. of Childr., Jan., 1926).

In the inquiry into possible allergic factors, every ramification of the patient's life, activities and surroundings must be gone into, and likewise the family history, since fully 50 per cent. of asthmatics give a positive family history of sensitization. A description of the onset, duration and termination of the attack should be obtained. The more clearly paroxysmal the attack, not induced by cough or exertion, the more likely is the case to be allergic (Kern).

Cases of asthma developing in childhood and adolescence are practically all allergic. Of those developing under 25 years, 50 per cent. are sensitive; under 35 years, 25 per cent., while of those appearing after 50 years, very few are allergic. Recent figures place the incidence of food asthma well under 5 per cent. Aside from the positive skin test, there must be clinical proof that exposure to a particular food will cause an attack. Of 125 cases, 22 reacted to 1 or more foods, but in only 5 was there any relation between food and disease, and in only 2 of these did a food cause asthma. The foods most commonly responsible are egg, milk and the cereals; next, shell fish and fruits. Drug allergies usually appear as urticaria or angio-neurotic edema, less often as asthma. Among the inhaled allergens those

most often to blame are the hair or dandruff of horses and cats and the feathers (goose, chicken) of pillows. Rabbit hair is often used in pillows. Other causes are duck, canary and parrot feathers; dog, guinea-pig and camel (women's hair puffs) hair, and sheep wool. Of hay fever cases, due to pollen, 40 per cent. suffer from asthma. A baker may become sensitive to the proteins of flour, a tailor to wool, an apothecary to powdered drugs, jewel polishers and woodworkers to wood dusts, especially boxwood. Orris root face powders may give trouble. Commonly there is sensitiveness to bedroom dust, at times from feathers or a wool or grass rug. Dust cases are extremely common. In 40 per cent. of 125 cases the author obtained positive skin tests to the patient's own or a stock dust extract, and in 26 per cent. the etiologic relation was clinically proven. Asthmatics commonly date the onset of their trouble to an acute respiratory infection; the inflamed mucosa, it would seem, offers a portal of entry for the sensitizing dose of a foreign protein. R. A. Kern (Ann. of Clin. Med., Sept., 1923).

Case of a fruit and produce dealer in whom merely handling tomatoes and grape-fruit produced asthma by *inhalation*. Other cases showed that *cold* is often a primary factor, like a foreign protein, and not merely a contributory cause of asthma. These are cases in which pollen or a food are known to be causative, yet the asthma returns in cold weather after their withdrawal, in the absence of bronchitis or heart disease. The cold acts so promptly as to preclude bacterial action as an explanation. Urticaria and even subcutaneous hemorrhages may similarly be induced by cold. In 1 case asthma was found due to sensitiveness to *mice*. Smelling a mouse—without knowing its presence—in a gauze-covered box brought on violent asthma and dermatitis of the exposed parts in 3 minutes; extermination of the rodents—several dead ones being found beneath the bed-room flooring—resulted in free-

dom from asthma for 3 years, until the patient moved to another house, facing a park. W. Lintz (Ann. of Clin. Med., Mar., 1924).

Close investigation of early attacks is important in the diagnosis, as later attacks may be induced by non-specific factors. A history of eczema in early childhood points to food asthma. Children are often sensitive to rabbit hair, used in upholstering, etc. A valuable diagnostic method consists in having the patient carry a cover-glass treated with glycerin, upon which substances floating in the air inhaled by him will collect. P. Schonwald (North-west Med., May, 1924).

Hyperemia and edema are produced by all asthmogenic substances. Asthma is a species of urticaria of the bronchial mucosa. In a boy extremely sensitive to egg, accidental inhalation of a little egg powder caused, in succession, edema of the mouth and lips, severe coryza, hoarseness and stridor, and an asthmatic attack. This patient had reacted by nausea and vomiting to the least amount of egg ingested, but had been enabled, by ingestion of gradually increasing amounts of egg powder in capsules, to take up to 5 Gm.; yet the accidental inhalation brought on the severe reaction above described. K. Baagöe (Ugeskr. f. Laeger, July 31, 1924).

Where protein tests in asthma are negative or treatment based on hypersensitiveness to food or air-borne proteins proves unsatisfactory, the writers recommend the *diagnostic use of autogenous vaccines* in order to elucidate the infectious factor in the disorder. It is necessary to isolate and identify the organisms present in all possible foci of infection: Nasal cavity and sinuses, especially the antrums and ethmoids; infected adenoids; tonsillar crypts; pus, if present; sputum, and feces. Due consideration should also be given to apical dental abscesses, infected endometrium, seminal vesicles, prostate and urinary tract. Stained films of each original material should also be studied. Each test injection is made with a sterile tuber-

culin syringe and fine needle, and the amount of each vaccine injected is 0.01 c.c. The injections are made in a spiral row. Positive reactions are either early, appearing in 10 to 30 minutes and soon fading, or late, noticeable in 12 hours or less, and at their height on the 2d day. Either of these positive results calls for therapeutic use of the vaccine that caused it. Since vaccines made of ostensibly non-pathogenic germs have often yielded positive skin reactions and given relief when used in treatment, test vaccines should be prepared from all types of organisms recovered from the patient. Of 26 asthmatic cases treated with such vaccines, 23 were either completely relieved or much improved. W. S. Thomas, L. W. Famulener and M. De M. Touart (Arch. of Int. Med., July, 1924).

Sensitization among those who work with drugs has occasionally been found responsible for asthma.

Questionnaire sent to 14 drug manufacturing houses. The commonest cause of asthma in drug workers was found to be ipecac, and next to it podophyllin and pokeroor. The handling of emetine solution and vanilla beans causes urticaria of the forearms and hands. Rhubarb and lycopodium hypersensitiveness is exceptional. One worker was sensitive to inhalation of urease, derived from the jack or soy bean. M. M. Peshkin (Jour. Amer. Med. Assoc., June 7, 1924).

In some instances no sensitization to any external agent can be found. Among these are cases in which there appears to be hypersensitiveness to certain putrefactive products formed in the intestinal canal.

A number of cases, upon careful examination, do not fall into 1 of the groups of pollen, epidermal, food, dust or bacterial sensitization. An outstanding feature in these patients is a history of digestive disturbances—irregular diarrheas, periodic constipation, nausea, headaches, vomiting, and



sometimes urticaria. Generally examination shows indicanuria and putrefaction in the freshly voided stool (acid stool with excess of Gram-negative organisms). To these cases the writers apply the term *endogenous asthma*. They may be recognized in that they give a reaction 2 or 3 times more intense than normal when a scratch test with 1:10,000 histamine (C. P., Kahlbaum) solution is carried out. The resulting wheals are 1.5 to 3 cm. in diameter. Two cases responded to therapeutic injections of histamine, but better results were obtained with biweekly **peptone** injections which, out of 10 cases, improved 8 and cured 2. Prevention of intestinal stasis is essential, and **colonic irrigations** and measures tending to a simplification of the intestinal flora are also indicated. M. A. Ramirez and A. V. St. George (Med. Jour. and Rec., Jan. 16, 1924).

The allergic origin of asthma has so absorbed attention that there has been a tendency to overlook all other etiologic factors. It seems necessary still to bear in mind as possible factors the group hitherto associated with reflex action originating in lesions of organs other than the lungs, *e.g.*, of the eyes, ears, upper respiratory tract, stomach, intestines, genitourinary system, etc. While in some instances disturbances of these organs no doubt act through allergy, in other instances this does not appear to be the case. Prominent in this connection are nasal obstructions or deformities, septal spurs, and hypertrophies of the turbinate mucosa. Nasal reflex points are especially to be found in the lower and middle turbinates.

The older conception of sensitive areas in the nasal mucosa, thought to cause asthma reflexly, is recalled by the writer. Slight stimulation of the nasal mucosa of an asthmatic by

means of a weak faradic current during an interval between attacks and while ausculting the lungs will cause the vesicular murmur of respiration to become more marked and piping; rattling may even be heard from a distance. This does not occur in a normal subject. All patients who presented this reaction showed some abnormalities in the nose or throat, verifying the belief that the asthma was of reflex origin. Henkes (Nederl. Tijdsch. v. Geneesk., Apr. 15, 1922).

Case of asthma of genital origin in a man of 32. Each intercourse was followed in 2 or 3 days by a typical attack persisting for 3 days. Complete recovery followed 5 **cauterizations of the inferior turbinate**, which are thought to have interrupted a double reflex arc, genito-nasal and naso-pulmonary. Strominger and Birman-Bera (Jour. d'urol., June, 1924).

The so-called "dyspeptic asthma," which may occur during the process of digestion and be attended with cyanosis, should also be mentioned. Sometimes this disturbance manifests itself during digestion only if some exertion is made. Treatment of any gastric disorder present will arrest the paroxysms.

Irritability of the pneumogastric nerve following whooping-cough, measles or infantile bronchial disorders, or due to pressure of enlarged bronchial glands upon the nerve, is another possible causal factor. Cases of asthma from chronic appendiceal disease operating through abnormal vagus irritability have been described.

Four cases in which asthmatic attacks disappeared after **appendectomy**. The asthma in such cases is ascribed to an abnormal irritability of the vagus due to chronic appendiceal disease, this irritability leading to asthmatic seizures when any disturbance of colloidal equilibrium is added. Pressure on the ileocecal region will also

bring on an attack. In 1 case attacks had been induced by antipyrin before operation; after the appendectomy antipyrin caused no disturbance. R. A. Gutmann (*Presse méd.*, Jan. 24, 1923).

According to some, a predisposing as well as an exciting factor is necessary for the production of asthma. Thus, according to Daniélopou, the presence of a local lesion, of tuberculous or other nature, constitutes an indispensable predisposing factor. Pottenger has laid stress on a relative increase of potassium as compared with calcium ions in the cells.

The idea of sensitization, while a great advance in our conception in the etiology of asthma, cannot be considered as the only factor active in the production of paroxysms. There is something in the make-up of the asthmatic which makes him susceptible to the action of proteins, reflex stimulation, climatic change and physical and chemical irritants. The condition of the body cells themselves determines to a marked extent the manner in which they will react to nerve and chemical stimuli. Experimenters have established beyond doubt the interdependence of the sympathetic nerves and calcium ions in the cell on the one hand, and the parasympathetic nerves and potassium ions on the other. Increased parasympathetic action (as expressed in bronchoconstrictor vagus overactivity in asthma) presupposes a relative increase in potassium as compared with calcium ions in the cells. Vagotonia should be conceived of as based not merely on parasympathetic hypersensitiveness but also on disturbed ion balance in the cells, so that the latter react to a morbid extent when the parasympathetic nerves are stimulated. Calcium, an integral part of the cell and necessary to sympathetic nerve action, may therefore be expected to be of value in asthma as well as in other conditions with parasympathetic hyper-irritability, such as hay fever, urticaria, serum

disease, spastic colon and diarrhea. F. M. Pottenger (*Amer. Jour. Med. Sci.*, Feb., 1924).

Endocrine disturbances are accepted by many as factors predisposing to asthma. T. Drummond (*Brit. Med. Jour.*, Feb. 24, 1923) has presented evidence in support of the view that adrenal inadequacy is a cause of it.

**PROGNOSIS.**—The prognosis of asthma depends upon the nature of its underlying cause. Cases of allergic asthma in which the cause can be discovered and eliminated, or of reflex asthma in which the primary disorder is easily reached and properly treated—such as nasal hypertrophies, polypi, aural growths, etc.—are frequently cured and remain so. The prognosis is best in young subjects with well-formed chests and in whom direct heredity cannot be traced. Where the above-mentioned favorable circumstances do not exist, the chances of recovery are limited.

Death rarely ensues from spasmodic asthma, but its complications may prove fatal.

**TREATMENT.**—The treatment of asthma consists of (1) arrest of the paroxysm; (2) preventive and curative treatment in the intervals between paroxysms.

**I. THE PAROXYSM.**—The fact having been ascertained that true bronchial asthma, and not cardiac asthma, exists, small doses of **morphine sulphate**, or 10 minims (0.6 c.c.) of **Magendie's solution**, given hypodermically, are among the most certain agents when rapid effects are necessary.

**Morphine** may be combined with **atropine** (not more than  $\frac{1}{20}$  grain—0.00054 Gm.—being given in any case). **Atropine** alone has been

urged as an excellent agent to arrest an attack.

In a study of the action of various drugs on the bronchi by the "direct method," that is, on excised surviving bronchial preparations of the pig, the most powerful bronchodilators were found to be (1) **papaverine** and various **benzyl compounds**, which act on the muscle cells; (2) **atropine**, which exerts its action through paralysis of the parasympathetic myoneural junctions, and (3) **epinephrin**, which produces active stimulation of the true sympathetic dilator terminals. The iodide, bromide, and nitrite ions produced a relaxation of the bronchial muscle. This effect, however, is probably considerably minimized in the intact body. Macht and Ting (*Jour. of Pharm. and Exper. Therap.*, Dec., 1921).

**Codeine** may be used instead of the morphine if the latter produces nausea. These remedies present, as objections, however, the partial suppression of expectoration in some cases, a certain amount of danger in cases of Bright's disease, and above all, in the case of morphine, the possibility of drug addiction unless strict control can be exercised.

The adrenal active principle, **epinephrin**, or **adrenalin**, is very effective. The best effects are obtained by injecting 5 to 10 minims (0.3 to 0.6 c.c.) of the 1:1000 solution in 1 dram (4 c.c.) of saline solution intramuscularly.

The writer used **adrenalin** in 22 cases of asthma and, with 1 exception, obtained good results. In this 1 exception, there may have been a complicating emphysema. In other cases the patients were always relieved within 20 minutes. Small doses, 2 drops or even 1 drop, proved usually efficient without the by-effects produced by larger doses. Relief was always experienced within 20 min-

utes. Triviño (*Revista Ibero-Americana*, Apr., 1918).

An attack of asthma can be cut short by the injection of **adrenalin** more rapidly than by any other method. In many cases 1 minim (0.06 c.c.) of 1:1000 adrenalin chloride is enough, more than 2 minims (0.12 c.c.) being rarely required. The injection should be given at the beginning of an attack. Such small doses give rise to no unpleasant sensations, such as frequently follow the injection of 3 or more minims. Treatment can be continued for long periods without any fear of ultimately causing arteriosclerosis. It is the only form of injection which a patient should be allowed to use on himself. A. F. Hurst (*N. Y. Med. Jour.*, Mar. 15, 1922).

Where **adrenalin** fails to relieve an attack, apparently because vagus excitation is such as to prevent the usual effect from stimulation of the sympathetic by the adrenalin, combined use of **atropine** and adrenalin is sometimes effective. The atropine is given first, to pave the way for the action of the adrenalin. L. von Gordon (*Schweiz. med. Woch.*, Dec. 6, 1923).

The writer deems it unwise to temperize by giving less than 1 c.c.\* (16 minims) of **adrenalin**, which amount he finds absolutely safe. Lintz (*Ann. of Clin. Med.*, Mar., 1924).

**Ephedrin**, the active principle of a Chinese plant known as Ma Huang, has been substituted for adrenalin, over which it has the advantage of full efficacy when given by the mouth.

**Ephedrin**, given by mouth to 20 asthmatics, gave relief in all but 3, and is an important substitute for epinephrin as a palliative remedy. Its effects are more prolonged than those of epinephrin, and there is absence, in most cases, of tremor and palpitation as by-effects of doses sufficient to relieve bronchospasm. Its effects by mouth are less rapid (30 minutes) than those of epinephrin given hypodermically. The relief lasts 4 to 24 hours. The dose employed was usually 0.05 Gm.

( $\frac{3}{4}$  grain) in adults. W. S. Thomas (Amer. Jour. Med. Sci., May, 1926).

**Pituitary extract, anterior lobe**, has been used with asserted benefit by Warfel.

The writer reports 7 cases of bronchial asthma treated with **pituitary body** anterior lobe on the plea that the paroxysms might be due to deficient adrenal secretion. One  $2\frac{1}{2}$ -grain (0.16 Gm.) tablet was given 4 times each day. Each case treated showed very marked improvement in the distressing train of symptoms in 48 hours. The duration of this treatment varied from 10 days to 7 weeks, but in no instance did it fail to make the patient comfortable in a short time. Warfel (Indianapolis Med. Jour., July, 1915).

Combined injections of 0.0008 Gm. ( $\frac{1}{80}$  grain) of **adrenalin** and 0.04 Gm. ( $\frac{2}{5}$  grain) of **pituitary extract** in 1 c.c. (16 minims) of water were used with marked success by Weiss in arresting paroxysms in 300 cases. The combination was more effectual than **adrenalin** alone. A second injection was required in only 10 instances.

**Chloral hydrate** also affords prompt relief; 15 to 20 grains (1 to 1.3 Gm.) may be given to an adult.

**Paraldehyde**, 30 minims (2 c.c.) hourly until improvement is noted, has been recommended.

**Chloroform** proves rapidly effective in some cases. Fifteen drops of it in a half-tumblerful of water to which a teaspoonful of syrup of orange-peel has been added make up a palatable dose. **Chloroform anesthesia** will also arrest the paroxysm, but it is not to be recommended unless other means have failed. A preliminary application of a 5 per cent. solution of **cocaine** to the nasal mucosa may aid in arresting the paroxysm and reduces the danger incident upon the administration of the anesthetic.

**Ether**, 30 to 40 drops (0.65 c.c. to 0.87 c.c.), may also be administered by the mouth as above, or on a piece of sugar, but the sudden volatilization produced by the heat of the stomach causes unpleasant eructations.

**Hoffmann's anodyne**, 1 dram (4 c.c.) in half a tumblerful of pure water, is frequently effective. The dose should be repeated every half-hour. **Aspirin**, 15 grains (1 Gm.), may be useful when any of the agents enumerated above are not available.

The application to the mucous membrane of the nasal cavities of a 5 per cent. solution of **cocaine** was highly recommended by Dieulafoy.

The **smoke** obtained from antispasmodic remedies—**niter**, **stramonium**, **tobacco**, **hyoscyamus**, and **belladonna**—is efficacious in cases in which emphysema is not marked.

Cigarettes may be made of paper soaked in a saturated solution of **nitrate of potassium** and **belladonna**. The sheets are allowed to dry, and are then rolled into the shape of cigarettes.

Sawyer recommends the following **fuming inhalation**:

℞ *Potassii nitratis*,

*Pulv. anisi fruct.* . . . .āā ʒss (15.5 Gm.).

*Pulv. stramonii fol.* . . . .ʒj (31 Gm.).

M. et ft. pulv.

A thimbleful of this, finely powdered, is placed on an earthenware plate, pinched by the fingers into a pyramidal shape, and lighted at the top. It burns with a smoldering and gently deflagrating flame, and is held near and beneath the patient's face, who breathes in the smoke.

An effective cigarette may also be made of equal parts of **lobelia**, **stramonium**, and **green-tea leaves**, or of **stramonium leaves** and ordinary **tobacco**. Tobacco sometimes proves

useful alone where it has not been previously used.

The local application of **epinephrin inhalant**, which is available in small, compressible tubes similar to those used for oil pigments, and the tip of which can be inserted deeply into the nostrils, is often very efficient.

The inhalation of 1:1000 **adrenalin solution** in a special very fine spray from a small atomizer arrests a paroxysm at any time. In established severe attacks, the following combination is recommended: **Adrenalin solution** (1:1000), 9 c.c. ( $2\frac{3}{4}$  drams); **atropine sulphate**, 0.01 Gm. ( $\frac{1}{8}$  grain); **cocaine hydrochloride**, 0.025 Gm. ( $\frac{3}{8}$  grain); distilled water, 1 c.c. (16 minims). Staubli (Münch. med. Woch., Jan. 21, 1913).

In infants in whom the attacks resemble capillary bronchitis, steam impregnated with **creosote** acts satisfactorily, according to La Fetra. In older children the **nitrate vapors** with or without stramonium are efficient. **Atropine** in doses of  $\frac{1}{200}$  grain (0.0003 Gm.) every two hours until the face flushes frequently produces a prompt cessation of the spasms. After the attack has passed off, the atropine is given twice or 3 times a day for several days. For long-standing cases and those in older children the following may be given:—

**R** *Potassii iodidi* . . . . gr. xx (1.29 Gm.).  
*Morphina sulphatis*. gr.  $\frac{1}{2}$  (0.021 Gm.).  
*Tinct. belladonnae* . . . . . ℥xx (1.23 c.c.).  
*Spts. atheris comp.* f3ij (12 c.c.).  
*Aqua* . . . . . q.s. ad f3ij (62 c.c.).—M.

The famous hyoscyamus and stramonium cigarettes of Espic are composed of the following agents:—

**R** *Belladonna leaves* . 6 grs. (0.39 Gm.).  
*Hyoscyamus leaves*,  
*Stramonium leaves*,  
of each . . . . . 3 grs. (0.19 Gm.).  
*Extract of opium* .  $\frac{1}{4}$  gr. (0.016 Gm.).  
*Cherry-laurel water*. q. s.—M.

The most active principle in some of the cigarettes used being pyridine, cigarettes may be replaced by inhala-

tions of this drug, 10 to 15 drops (0.6 to 0.9 c.c.) being inhaled from a handkerchief. The following method of using pyridine, however, is the most effective:—

The patient being in a small room, a saucer containing pyridine is put some distance from him. He is allowed to inhale the fumes about half an hour.

**Hyoscyamine**,  $\frac{1}{40}$  to  $\frac{1}{20}$  grain (0.00048 to 0.00055 Gm.) hypodermically, has been recommended by S. Solis-Cohen and others.

Passion flower (*passiflora incarnata*) possesses hypnotic and antispasmodic powers. It possesses peculiar value in allaying asthmatic paroxysms and in preventing their full development. It may be given in tincture or fluidextract. The dose is from 10 to 30 minims (0.6 to 1.8 c.c.) well diluted and given from every ten minutes to every half-hour until relief is experienced, emesis caused, or drowsiness induced. Half a fluidounce (15 c.c.) of the fluidextract has personally never been exceeded in the course of two hours. Patients have fallen asleep after 6 doses of 10 to 20 drops (0.6 to 1.2 c.c.) each, given every ten or fifteen minutes, or after a single dose of 1 fluidram. In 2 out of 8 cases its use produced but slight mitigation of distress, and was abandoned. In 6 cases which had proved rebellious to other methods it gave prompt relief. S. Solis-Cohen (American Medicine, Sept. 14, 1901).

Of the remedies employed to ward off an attack, **caffeine iodide** the most useful. For patients who cannot take even the smallest amounts of iodide without symptoms of iodism, the writer gives 5 to 10 grains (0.32 to 0.64 Gm.) of **calcium chloride** before or after the caffeine iodide. They cannot be dispensed together, as calcium iodide is formed and the calcium no longer controls iodism.

Other combinations of value are:—

I.

℞ *Nitroglycerin* ..... gr.  $\frac{1}{200}$  to gr.  $\frac{1}{100}$   
(0.0003 to 0.0006 Gm.).

*Sodium iodide* ... gr. iij to gr. v  
(0.2 to 0.3 Gm.).

One dose to be repeated every two or three hours until the attack subsides.

II.

℞ *Sodium nitrite* ..... gr. ss to gr. j  
(0.032 to 0.065 Gm.).

*Sodium iodide* ... gr. iij to gr. v  
(0.2 to 0.3 Gm.).

Give every two or three hours.

III.

℞ *Fluidextract of grindelia robusta* .. ℥xv to ℥xxx  
(0.9 to 1.8 c.c.).

*Sodium iodide* ... gr. ij (0.13 Gm.).

*Nitroglycerin* ..... gr.  $\frac{1}{200}$  (0.0003 Gm.).

*Tincture of euphorbia pilulifera* ℥xx (1.2 c.c.).

*Spt. of chloroform*  
q. s. ad .. 3j (4 c.c.).

M. Sig: One to 2 teaspoonfuls in water every two to four hours while the attack lasts.

Morphine may be given hypodermically in conjunction with hyoscine, as in the following:—

℞ *Morphine hydrochloride* . gr.  $\frac{1}{6}$  (0.01 Gm.).

*Hyoscine hydrobromide* . gr.  $\frac{1}{200}$  to gr.  $\frac{1}{100}$   
(0.0003 to 0.0006 Gm.).

To the foregoing,  $\frac{1}{200}$  grain of **nitroglycerin** may be added, or **atropine sulphate** may be substituted for the hyoscine.

As a useful form of vaporized spray solution the writer recommends the following:—

℞ *Cocaine hydrochloride*,  
*Atropine sulphate*,  
of each ..... gr. ij (0.13 Gm.).  
*Sodium nitrite* .. gr. x (0.65 Gm.).  
*Glycerin* ..... ℥xx (1.2 c.c.).  
*Rose water*, q. s. ad 3ss (15 c.c.).

M. et sig.: Five or 10 minims to be inhaled through the nose by means of a very fine vaporizing spray. Repeat at intervals of twenty to thirty minutes if necessary. P. W. Williams (Practitioner, Oct., 1910).

Constantly successful results in asthma from combined administration of **strontium bromide** in large doses and injections of **camphorated oil** 2 c.c. (32 minims). As a preliminary measure, salt should be at least in part proscribed from the diet. In adults the daily dose of the bromide is 4 Gm. (1 dram); occasionally as much as 6 Gm. (1½ drams) is required. On the first day, 2 injections of a 10 per cent. solution of camphor in oil, 2 c.c. (32 minims) at a dose, are given. Improvement occurs promptly, at times immediately. Camescasse (Presse méd., Dec. 20, 1917).

A 10 per cent. preparation of **strontium chloride-urea** known as stronturan used with favorable results. The usual dosage was one 5 c.c. (80 minim) ampule intravenously on alternate days, to an average total of 6 injections. Of 17 cases, 11 were regarded as cured after over a year's observation, 3 were improved and 3, unimproved. In 2 cases, attacks ceased after the 2d injection. A. Kempinski (Deut. med. Woch., Sept. 18, 1925).

Intravenous injections of **calcium chloride** have been recommended by Pottenger. The drug had already been found somewhat useful by the mouth by Kayser.

Calcium salts being sedatives of the nervous system, it was tried with suc-

cess in 13 cases of asthma and allied conditions. It was given in the form of 20 Gm. (5 drams) **calcium chloride**; 40 Gm. (10 drams) simple syrup, and distilled water, to 400 Gm. (13 ounces). The patient took a tablespoonful of this in milk every two hours for eight days. No untoward by-effects were observed in any instance, and the patients all said that after a day or so they could breathe and expectorate easier and their sleep was no longer disturbed. After the third day there were no further attacks in all but 2 cases. Kayser (*Therap. Monats.*, March, 1912).

Intravenous injection of 5 to 10 c.c. (80 to 160 minims) of 5 per cent. **calcium chloride** solution recommended. The injection should be made slowly, taking 4 to 5 minutes for 10 c.c. Three severe cases are reported in which the measure relieved both the bronchial spasm and the secretion. In 1 case the relief of heart strain, with slowing of the pulse, was almost phenomenal. The number of doses given ranged from 4 to 14, given at intervals of 2 or 3 days at first, later at longer intervals, up to 1 week. None of the injections exceeded 5 c.c., except in the case receiving 14 injections, in which the last 8 or 9 doses were of 10 c.c. each. F. M. Pottenger (*Amer. Jour. Med. Sci.*, Feb., 1924).

Good results from administering 0.3 to 1 Gm., or exceptionally 1.5 Gm., of **calcium chloride** intravenously in a 5 or 10 per cent. solution. One or 2 injections were sufficient to check an acute attack. A course of 7 to 10 injections being then given, the patients had no further attacks for several months. Judging from the oculocardiac reflex, vagal irritability is not decreased by the calcium, the action of which must therefore be exerted at some point other than the vagus. Petzetakis (*Bull. Soc. méd. des hôp. de Paris*, Apr. 10, 1924).

**Antipyrin**, 15 grains (1 Gm.), given every 3 hours until the attack is relieved, has seemed especially effec-

tive in anemic cases; but such large doses are toxic in some cases.

**Citrated caffeine**, 1 to 5 grains (0.065 to 0.32 Gm.), dissolved in warm water, every 4 hours—is effective in bronchial asthma and bronchitis associated with spasm of the bronchial tubes. **Theobromine** has also given good results.

**Theobromine sodio-salicylate**, possessing a vasodilator action, is very useful in bronchial asthma, both in the so-called nervous type and in the catarrhal form of the affection. At the inception of the attack the writer prescribes 15 grains (0.9 Gm.) dissolved in water; if relief is not apparent in fifteen minutes a second dose is given; rarely is a third necessary. No tolerance to the drug is established, and it may be taken daily for a considerable period. Von den Velden (*Münch. med. Woch.*, xiv, 697, 1907).

**Theobromine** preparations recommended among the remedies serviceable in asthma. Hofbauer (*Wien. klin. Woch.*, Dec. 3, 1925).

**Nitroglycerine**, given in doses of  $\frac{1}{100}$  to  $\frac{1}{50}$  grain (0.00065 to 0.0013 Gm.), acts rapidly in some cases; but even in these its effects are frequently only temporary. From 2 to 5 drops of the 1:100 solution (if there is but little emphysema and no cardiac disorder) have been recommended.

**II. TREATMENT IN THE INTERVALS BETWEEN PAROXYSMS.—Hyposensitization.**—In the light of modern findings to the effect that bronchial asthma is due in very many instances to some form of hypersensitiveness, elimination of the latter assumes an important place in the treatment.

In this connection J. A. Clarke, Jr., divides the patients into 3 groups:

(1) Those in whom all the *atopens* [substances to which the patient is specifically hypersensitive] are known; (2) those partially diagnosed, in which some atopens causing asthma have been discovered, but one is convinced there are others; (3) those in whom neither the history nor the skin tests, etc., have revealed any atopens producing asthma. It is possible, according to Clarke, to make at least a partial diagnosis in over 75 per cent. of cases, and of these,  $\frac{3}{4}$  should be markedly relieved by elimination of the atopen or by hyposensitization.

Atopens with which the patient does not come in contact may be dismissed with a warning, explaining just where these substances are likely to be found. Elimination of the atopens causing asthma is the method of choice, but frequently is possible only at great inconvenience or economic loss. **Hyposensitization** is Cooke's term for lessening of hypersensitiveness by giving repeated, gradually increasing doses of the offending atopen. (The word desensitization should be reserved for true anaphylaxis.) Any extract which will produce a good-sized urticarial wheal in the skin reaction is potent for purposes of hyposensitization.

In treatment, the ideal initial dose is one which will just fail to produce constitutional symptoms, though producing locally an edema of the skin and subcutaneous tissues about 3 cm. in diameter and disappearing in 24 hours. When, in the intradermal test, 0.01 to 0.02 c.c. is used, it is usually quite safe to give as an initial therapeutic dose 0.1 c.c. of the weakest solution that will just give a weak but definite positive reaction. As regards subsequent increase in dosage, a safe rule is 50 per cent. increase at each injection for the earlier injections—say, the first 10—then more conservative increases. If the patient is exposed to and suffering symptoms from the atopen and the first injection gives some relief, it is usually safe to give the next injection when the improvement begins to subside. Otherwise, 5 to 7 days is a safe rule. When relief is com-

plete, repetition of doses will be required only when symptoms reappear; this may be as often as once a week, but more frequently is 1 to 2 months. In a few instances the maximum dosage available without the production of constitutional symptoms does not suffice to give clinical relief; these are unavoidable failures of hyposensitization.

Constitutional reactions from an overdose may be either immediate or delayed. Severe or dangerous reactions are always the result of carelessness or mistakes. The delayed reaction, beginning gradually within 24 hours, persisting 3 to 7 days, and featured by increased severity of the asthma, occurs with the higher doses and suggests that the maximum dose has been reached. Marked improvement usually follows it, and no more doses are given until the symptoms again increase in severity, when about  $\frac{1}{4}$  or less of the dose causing the reaction is given (Clarke).

Having made the diagnosis by the history and the cutaneous reactions, **removal of the offending proteins from the diet**, or from pathogenic environment, or **immunization** of the patient against such proteins as cannot be so controlled, are indicated. In mixed cases both methods may be necessary. From the author's experience, 75 per cent. of asthma cases in which the cause can be definitely determined can be improved. A. Vander Veer, Jr. (Amer. Jour. Med. Sci., July, 1922).

The writer finds it simpler to apply repeatedly to the skin—instead of injecting it—minute quantities of the protein to which the patient is susceptible. In a case of severe asthma from horse emanations, skin reactions from horse hair, induced almost daily for 2 months, brought relief. Vallery-Radot (Bull. Soc. méd. des hôp. de Paris, Mar. 23, 1923).

By skin tests with 38 proteins in a girl of 9 with asthma of 1 year's standing the cause was discovered to be cat's hair, all other substances being negative. An attack in the hospital occurred 7 hours after she had played with a kitten. In asthma of animal origin the best procedure is subcuta-



neous injections of the causative substance in minute, gradually increasing doses. In asthma due to food proteins, ingestion of the substance in minute, increasing amounts is advisable. K. Baagöe (Ugeskr. f. Læger, May 3, 1923).

In a study of 235 cases of proved asthma, excluding the pure pollenoses, the writer, using both stock dust extracts and extracts of dust from the patient's own environment, found dust atopens a primary asthmogenic factor in 57 per cent. Treatment included hypodermic injections of house-dust extract in doses of 0.1 c.c., increased by 0.1 c.c. weekly up to 1 c.c. This dose was repeated weekly, then at longer intervals as improvement occurred. Stock dust was used if it gave a good reaction, otherwise extract of dust of patient's own environment. Considerable improvement occurred in 62 per cent., slight improvement in 30 per cent., and no change in 8 per cent. Maximum benefit may be delayed several months. G. P. Meyer (Atlantic Med. Jour., Nov., 1923).

Some stubborn cases of asthma can be cured if one bears in mind that certain foods, particularly fruits, can produce attacks, not only after ingestion but also by inhalation; such food must not be handled as well as not eaten. When one suspects that a certain substance is responsible for asthma, but the cutaneous tests have proven negative, the tests should be repeated before and during the attack, and negative results will frequently turn out to be positive ones. Lintz (Ann. of Clin. Med., Mar., 1924).

Treatment based on discovery of the special irritant protein has been nearly always successful in the author's hands. Different proteins may be responsible in different members of a family. In Porto Rico the commonest cause of asthma is shell-fish. In the 30 per cent. of patients who did not respond to tests for hypersensitiveness, the treatment consisted of diet regulation, breathing exercises and autogenous vaccines. In 2 patients there was found a tuberculous condition at the

hilum, previously overlooked. Two others proved sensitive to a fungus in the sputum; 1 grew better under a vaccine made from this fungus. R. M. Suárez (Porto Rico Med. Assoc. Bull., Apr., 1925).

**Vaccines.**—In some cases the cause of asthma seems to lie in sensitization to bacteria, which can be located by culturing or skin tests, and are to be found frequently in the sputum, or else in material from infected sinuses, the pharynx or tonsils, excised or *in situ*, or, occasionally, in the stools. Hekman, *c.g.*, found numerous streptococci in 300 asthmatic sputums and believes asthma to be usually attended with sensitization originating in bacterial infection of the smaller bronchioles. Under these circumstances, treatment by autogenous vaccines is recommended.

Gradual desensitization with vaccine prepared from the sensitizing organism, determined by skin test, advocated. Immunization against infection with the same organism is also insured. The initial dose should not be more than 100 million bacteria, increased by 25 million every fourth day. The patient remains free for from 2 to 6 months, as a rule. If sensitization returns the case is more easily controlled the second time. The results obtained with vaccines in cases in which skin tests have determined the sensitizing bacterium are brilliant. In the non-sensitive cases the results are not so good, but still encouraging; about 60 per cent. of patients are relieved. M. L. Landman (L. I. Med. Jour., 1922).

Good results with streptococcic autogenous vaccines prepared from the patient's sputum, even without change of environment. The initial injection is 40 million bacteria, increased gradually to  $\frac{1}{2}$  or 1 billion, according to reactions. In obstinate cases a turpentine fixation abscess occasionally brings relief. Breathing exercises are useful.

J. Hekman (Nederl. Tijd. v. Gen., Dec. 15, 1923).

In preparation for the treatment of asthma with **autogenous vaccines**, the writers made cultures in 62 cases from various sources according to the indications in each case. Treatment was based on the positive results from the test vaccines, usually 2 or more organisms giving sufficiently active reactions to be used for this purpose. The treatment vaccines were separate suspensions of each organism in salt solution, plus 0.25 per cent. tricrosol, 1 c.c. containing about 1 billion organisms, except in the case of *Streptococcus hemolyticus* and the Friedländer bacillus, in which the concentration was halved. The object sought was to produce at frequent intervals a local reaction with slight swelling, tenderness and perhaps erythema, lasting 1 to 5 days. The initial dose was 100 million of each treatment dilution; if this produced the desired reaction it was repeated every 2 or 3 days until no reaction followed, whereupon the dose was increased by 100 million. The dosage seldom exceeded 400 million. With improvement the intervals were increased to 5 and then 7 days. The total number of doses was from 1 to 30, and the average 15. Complete relief or material improvement resulted in 87.1 per cent. W. S. Thomas and M. De M. Touart (Arch. of Int. Med., July, 1924).

**Bacterial vaccines** used in 144 cases of asthma, of which 51 per cent. were completely relieved; 39 per cent. improved in varying degrees, and 10 per cent. unimproved. G. T. Brown (Amer. Jour. Med. Sci., Jan., 1926).

A procedure of obvious importance in the treatment of asthma, and applicable in particular where the agent to which the patient is sensitive has been discovered, is the **removal of the exciting agent**. Thus, in food asthma, the exciting food should, if possible, be excluded from the diet. In the case of foods which are hard to exclude because of their being

present in many prepared dishes, *e.g.*, eggs, wheat and milk, an attempt at **hyposensitization** becomes necessary. As a rule, this need be carried out only for foods which give a positive skin test in 1:500 or higher dilutions. In applying the treatment, the initial dose injected is 0.1 c.c. of the highest dilution which does not cause a positive response. Ascending doses and declining dilutions are injected weekly until 1 c.c. of a 1:100 dilution fails to excite a response.

Similar procedures may be followed in asthma due to the horse, cat, dog or fowl. Generally beginning with a 100,000 dilution of the corresponding purified protein, weekly subcutaneous injections of 0.1, 0.2, 0.4, 0.6 and 0.8 c.c. are given, then like series of injections of 1:10,000, 1:5000, 1:1000 and finally 1:100 dilutions. If severe local or asthmatic reactions occur it may be necessary to repeat the same dose once or twice (Kolmer).

In food allergy, desensitization may also be effected by giving minute amounts of the dried food, *e.g.*, 0.001 or 0.0005 Gm., in a capsule 3 times daily, then gradually increasing the number of capsules and the amount in each until a considerable daily dose is being taken without reaction.

**Non-specific Therapy.**—Some observers advocate non-specific treatment, either in cases in which the offending protein cannot be discovered or likewise even in cases with known sensitiveness.

Weil found that the injection of **peptone** exhausts the anaphylactic mechanism and leads to desensitization irrespective of the nature of the sensitizing antigen. Since the desensitization is quite non-specific, skin tests for the causative specific antigen are not required. This can be

accomplished by a single large dose, but the effects are relatively short lived and better results are secured by small and increasing doses extending over a considerable period of time. In some cases the large initial dose may be required, followed by smaller and decreasing doses, but it is not the plan to be recommended. The dose of peptone stops the attacks for periods roughly proportional to their previous frequency; thus, if the attacks occurred weekly the remission should last from 6 weeks to 2 months, while freedom for 3 or 4 months should follow if the attacks occurred at intervals of 3 weeks. The only peptones to be used are Witte's or Armour's "ordinary" peptone, since these are the ones which contain sufficient of the primary proteoses. A 2 per cent. solution of Witte's or a 5 per cent. solution of Armour's are the most convenient for use. The peptone should be dissolved as far as possible in three quarters of the desired volume of normal saline by agitation and warming to 37° C. Then 1 c.c. (16 minims) of a 2 per cent. solution of **sodium carbonate** should be added for each 0.33 Gm. (5½ grains) of peptone to secure the requisite fineness of the suspension. The whole is then brought up to the desired volume with normal saline, adding **phenol** to 0.25 per cent. The initial dose should be about 0.3 c.c. (5 minims), which should be increased by about 0.2 c.c. (3 minims) every fifth day until 6 doses have been given, when the dose then reached should be continued for 3 or 4 more injections. Injections should not be given during attacks. A. G. Auld (Brit. Med. Jour., July 20, 1918).

Analysis of results obtained severally with specific desensitization, autogenous vaccines, milk or peptone in sensitive and in non-sensitive asthmatics led the writer to favor **non-specific therapy** more or less as a routine measure in asthma, even in the sensitive cases, except where removal of the offending protein gives relief.

In non-sensitive cases, **milk injections** relieved a larger percentage (6 out of 8 cases) than did **peptone** or **autogenous vaccine**. Milk is the non-specific agent of choice because of its ready supply and ease of preparation. The writer merely placed whole milk in a 2-ounce, rubber-capped bottle on a water-bath and allowed it to boil for 1 hour. The initial dose was 0.5 c.c. (8 minims), given subcutaneously. This was increased by 0.5 to 1 c.c. at tri-weekly intervals up to a maximum of 3 c.c. (48 minims). In non-specific protein therapy it is important to avoid anaphylaxis; this is done by testing for sensitiveness in the usual way with the skin test. N. S. Schiff (Amer. Jour. Med. Sci., Nov., 1923).

The **tuberculin** treatment of bronchial asthma tried in 150 patients. It proved entirely useless in 8; in 10 others there was slight improvement, but in the remaining cases recovery or considerable improvement resulted. Care was taken to prevent further attacks, and on the slightest indication of an impending attack of asthma 0.2 to 1 c.c. of **adrenalin** (1:1000) was injected subcutaneously. These injections were generally necessary only in the first few days. Great caution is urged. An active lung process must be excluded, and too large doses may readily cause severe attacks of asthma. The patients should, if possible, be treated for the first 10 or 14 days in a hospital. S. von Leeuwen (Münch. med. Woch., June 9, 1922).

Combined **peptone** and **vaccine** treatment recommended, especially in cases that do not respond to either agent alone. Three grades of the mixed solution were used: (A) 5 c.c. of 5 per cent. peptone + 235 million organisms mixed catarrhal vaccine; (B) 5 c.c. of 10 per cent. peptone + 940 million organisms; (C) 10 c.c. of 10 per cent. peptone + 1880 million organisms. For the first 4 weeks ½ tube of A was given weekly; the next 4 weeks, ½ tube of B, and so on. The injections were given intramuscularly in the "painless area" just below the anterior

superior iliac spine. Of 24 cases, 14 were cured, 4 greatly improved, 5 somewhat improved, and 1 not improved. A fairly sharp reaction usually followed the injections in about 6 to 8 hours. The best results were obtained in the younger patients. J. Veitch (Brit. Med. Jour., Jan. 5, 1924).

Improvement or cure obtained in 10 out of 13 asthmatics by **autohemotherapy**, 4 or 5 c.c. of the patient's own blood being withdrawn and re-injected subcutaneously in the arm or leg. The dosage was gradually increased to 8 or 10 c.c., and from 4 to 10 weekly injections were given. The patients ranged in age from 16 to 51 years. Carranza and Orgaz (Semana méd., Dec. 17, 1925).

**Drugs.**—By promoting thyroid efficiency, the **iodides** increase metabolic activity and may cure the disease, as personal cases have shown. They are best administered with **tincture of belladonna**, 8 minims (0.5 c.c.) to the dose, to sustain the immediate relief afforded and prevent the paroxysms. **Suprarenal gland** in 2-grain (0.13 Gm.) doses after meals is very helpful when the suboxidation, shown by cold extremities and weak pulse, persists.

When bronchial lesions are present, the treatment should begin by a course of **potassium iodide**, rapidly increasing the dose from 5 to 30 grains (0.3 to 2 Gm.) 3 times a day. To avoid, as much as possible, gastric disturbances, it should be administered in not less than a half-tumblerful of pure water at first, and in a tumblerful when larger doses are to be taken. **Fowler's solution**, 3 minims (0.2 c.c.) 3 times a day, generally counteracts the eruption and other unpleasant effects of the iodide, and should be administered simultaneously if need be. Potassium iodide is contraindicated in cases in which

there is a tendency to hemoptysis, or when there is an infraglottic disorder.

The author's experience has confirmed the curative value of **parenteral protein therapy** and of **benzyl benzoate and calcium chloride**. His formula is: 20 Gm. (5 drams) benzyl benzoate; 16 Gm. (4 drams) gum acacia; enough of a 50 per cent. solution of calcium chloride to bring the amount to 200 Gm. (6 $\frac{2}{3}$  ounces). Five times a day 10 c.c. (2 $\frac{1}{2}$  drams) are inhaled, using an ordinary inhaler. **Psychotherapy** is a valuable adjuvant, also **refraining from meat, fish, beans and peas**. He has had patients lose their asthma completely on a **purin-free diet**, without other measures. Van Leeuwen (Nederl. Tijds. v. Gen., Feb. 5, 1921).

A deficit of calcium in the blood serum was found in some asthmatics by the writers. **Calcium lactate** alone by the mouth failed to give relief, but when combined with **thyroid extract** it gave relief in 48 to 72 hours in 6 out of 12 cases. The dose of the calcium salt was 5 grains (0.3 Gm.) and of the thyroid,  $\frac{1}{4}$  grain (0.015 Gm.), at first 3 times daily, and later reduced to twice or even once a day. Return of symptoms occurred when the medication was discontinued, but added use of the **ultra-violet ray** from the **mercury vapor quartz lamp** appeared to fix permanently the ionic calcium content of the blood serum. F. J. Novak, Jr. and A. R. Hollender (Jour. Amer. Med. Assoc., Dec. 15, 1923).

During the interval the best remedies are **tincture of belladonna** and a saturated solution of **calcium iodide**—the latter given in doses of 1 dram (4 c.c.) 3 times daily after meals. In cases of severe, prolonged asthma, lasting for days and very difficult to check, a **foreign protein intravenously** will usually succeed, *e.g.*, 4 minims (0.25 c.c.) of **typhoid vaccine** intravenously, given on 2 successive days. Lintz (Ann. of Clin. Med., Mar., 1924).

An important feature is to insure free action of the intestines. **Olive**

oil, 4 ounces (120 Gm.) injected into the rectum on retiring, and kept therein until morning, will insure an evacuation.

Asthenia may be said to be present in all cases of asthma. This is met most satisfactorily by **strychnine** in increasing doses, beginning for adults with  $\frac{1}{60}$  grain (0.0011 Gm.) after each meal and gradually bringing the dose up to  $\frac{1}{20}$  grain (0.0032 Gm.) during a period of 2 months.

In a paper based on 140 cases, the writers urge anew that one factor which helps and perhaps augments an asthmatic attack is the lessened alkalinity of the blood and tissues, and that the administration of large doses of **sodium bicarbonate** or **sodium citrate**, until the reaction of the urine is blue to litmus, seems to be an essential part in the treatment. While the urine was kept alkaline, nearly all their cases were treated with subcutaneous or intramuscular injections of **soamin** (a sodium arsanilate) used at first in 1-grain (0.065 Gm.) doses, then after 4 days  $1\frac{1}{2}$  grains (0.1 Gm.), and so on until the dose was increased to 5 grains (0.3 Gm.). Three or 4 weekly injections of 5-grain (0.3 Gm.) doses completed the course. Nearly 96 per cent. of cases so treated were relieved, and 75 to 80 per cent. were cured. Any disorder that may serve as the starting point of an attack, including lues or tuberculosis, should be adequately treated. Roy and Bose (Calcutta Med. Jour., June, 1918).

Fatigue and vagotonia were determined to be the factors in the production of the bronchial spasm and associated bronchitis in one of the author's cases. The injection of  $\frac{1}{20}$  grain (0.003 Gm.) of **pilocarpine hydrochloride** was helpful in recognizing this type, and **atropine** relieved attacks when it was administered by mouth in  $\frac{1}{400}$  grain (0.0006 Gm.) doses. Lambright (Ohio State Med. Jour., Apr., 1922).

The treatment in undiagnosed cases or in the undiagnosed factors of the partially diagnosed cases consists in **elimination of all foci of infection**, particularly in the nose and throat. The nasal passages must be made functionally sufficient. A **sputum vaccine** made from washed sputum should be tried, but must be properly prepared, the important organisms being grown separately and mixed later. If such a vaccine cannot be procured, a good **stock vaccine** is preferable. The most useful drug is **sodium iodide**. **Epinephrin** for the attack itself is best, and can be injected promptly by the patient himself. Inhalation of smoke of burning **stramonium** and **belladonna** is very useful. **Benzyl benzoate** and **acetylsalicylic acid** relieve in a few cases. Overeating, particularly of proteins, should be advised against, every effort made to prevent catching cold, and dusty atmospheres avoided. J. A. Clarke, Jr. (Ann. of Clin. Med., Sept., 1923).

When the asthma occurs in connection with pregnancy **viburnum prunifolium** has been regarded as a valuable remedy. If there should be any indication of abortion, **chloral hydrate** may be administered simultaneously.

**Organotherapy.**—**Pituitary extract**, posterior lobe, was recommended in 1910 by S. Solis-Cohen, who found it most effective when injected hypodermically, though useful also when given by the mouth. Léopold-Lévi reported in 1912 good results from **thyroid gland** in 23 severe and long-standing cases. These agents probably do good by promoting the destruction of irritating wastes tending to induce bronchospasm. I find 1 grain (0.065 Gm.) of thyroid 3 times daily necessary to obtain satisfactory results. Large doses, by promoting excessive tissue waste, do more harm than good. **Corpus luteum** and other

**ovarian** preparations have also been used with favorable results in certain cases.

In many cases of asthma occurring during the menopause, natural or artificial, the administration of **corpus luteum** relieves the dyspnea along with the other symptoms of the menopause. Fishberg (Med. and Surg., Jan., 1918).

Case in which asthma followed rapidly upon the production of an artificial menopause by radium. No sensitization could be discovered, and for a year all treatment failed. **Ovarian** and **mammary extracts** being then given, the asthma ceased in 3 days, and had not returned 11 months later. Ross and Rolleston (Brit. Med. Jour., Jan. 7, 1922).

Case which appeared to be of ovarian as well as hypothyroid origin. Daily doses of 0.3 Gm. (5 grains) of **thyroid extract** caused the manifestations of myxedema to recede, and the dyspnea finally disappeared almost entirely in a few days. Ten days later the prolonged inhalation of the odor of roses, to which she was sensitive, produced absolutely no effect. The experiment was continued for 6 months. As long as the organotherapy continued, the patient was free from all respiratory and other phenomena; as soon as it was suspended, both the myxedema and the respiratory disturbances reappeared. Vidal, Abrami and de Gennes (Presse méd., May 6, 1922).

Case of mental disturbance which was diagnosed as cerebral anemia due to menorrhagia. The menopause was artificially induced by introduction of radium into the uterine cavity. In 10 days she was mentally normal and menstruation ceased permanently, but there followed purulent secretion from both antrums which had been previously diseased, and severe asthmatic attacks. These attacks were cured by **ovarian organotherapy**. J. N. MacBean Ross (Brit. Med. Jour., Jan. 7, 1922).

Some cases of asthma may be due to adrenal disturbances, resulting in

hypotonicity of the sympathetic; this condition is relieved by giving **adrenalin**. With the lowered sympathetic tone may be combined increased irritability of the vagus terminals in the bronchi, due, in turn, to decrease of blood calcium because of parathyroid insufficiency. This latter condition is one of the chief causes of the unsteady vagus-sympathetic equilibrium underlying asthma. L. von Gordon (Schweiz. med. Woch., Dec. 6, 1923).

Out of 14 cases of asthma of the capillary bronchitis type in children 3 to 8 years old, 13 were completely cured by **thyroid gland**, 0.03 to 0.05 Gm. ( $\frac{1}{2}$  to  $\frac{3}{4}$  grain) daily, kept up for some months. Some of the patients had no further attacks as soon as the drug was started. The 1 child in which it failed had horse asthma, and later died when given an injection of diphtheria antitoxin. Gonzalez Meneses (Arch. españ. de ped., Jan., 1926).

#### **Non-pharmaceutic Measures.**—

**Static electricity**, by stimulating the peripheral vasomotors, enhances the action of strychnine when the latter is given in asthma. Daily sittings of 15 minutes each are required to sustain the beneficial effects obtained. The **high-frequency current** has also been used with success.

Hydrotherapy in the form of cervical or spinal cold douches has been advocated. The **sudden application** of a jet of **cold water** to the back of the neck may control an attack of asthma.

The barrel-chest, when due to the disease, is only met with in advanced cases. But, whether present or not, the conditions acting as its causes are generally present, *viz.*, weakness of the respiratory muscles, including the diaphragm. The treatment of all cases should, therefore, include measures designed to increase nutrition of these muscles and the activity of

their nervous supply. **Strychnine** fulfills the latter objects, but must be assisted by complementary measures designed to localize, as it were, its beneficial influence.

For the superficial muscles of the chest, **massage**, first along the intercostal spaces, then over the large muscles, the deltoids especially, is indicated; the outline of the muscles should be borne in mind and the active pressure exerted along the muscular fibers toward the arterial trunk supplying each set. For the diaphragm the **faradic current** alone is of service, the negative pole being applied over the course of the phrenic nerve just above the clavicle and the positive over the xiphoid cartilage. The sponges being fully moistened with salt water and applied, the patient is directed to empty his lungs of air, then to *inflate them only partially*, and to continue this restricted respiratory act during the entire sitting, —about 5 minutes at first, then 10 minutes. The oftener this procedure is undertaken, the sooner will satisfactory results be attained.

At home the patient will enhance the effects produced by a daily **calisthenic exercise**, consisting in bringing the fists up to the shoulders and approximating the elbows anteriorly as much as possible with each expiration. Chairs have been invented by means of which the exaggerated expansion of the thorax may be counteracted.

The patient should also be taught to obtain control over his respiratory muscles. As stated by Talma, the spasm of the respiratory passages may be produced voluntarily by the majority of asthmatic patients and by many normal individuals. Almost

all asthmatics can control the spasms even during an attack, but certainly during the period of remission. The muscles of the respiratory passages are either under the control of the will or may be brought under such control. As a consequence of these conclusions the importance of **respiratory gymnastics** for asthmatic patients is patent. The number of respirations per minute must be reduced and expirations performed slower and more completely. The spasm of the muscles will thus be controlled. The speech must be regulated, and while speaking the patient must inspire slowly and deeply. The asthmatic must learn to maintain the proper tension of the muscles of the neck, chest, and abdomen.

**Compressed air**, the patient being placed in pneumatic air-chamber in which the air has been condensed, is of great value in bronchial asthma and secondary emphysema. Unfortunately, the apparatus required is so bulky and expensive that it is hardly ever at the disposal of the physician. Expiration into rarefied air is of signal value in spasmodic asthma, the apparatuses of Waldenburg and Solomon Solis-Cohen being especially efficient for the purpose. I employ the **Guillemin hydraulic apparatus**, owing to the fact that no weights are required and because its diminutive size causes it to occupy but little room as compared with other instruments.

**Radiotherapy.**—The **X-rays** have been used by a number of observers, chiefly over the spleen and hila of the lungs, with asserted good results. According to Waldbott, only the anaphylactic type of asthma is benefited by this treatment.

With small doses of **X-rays**, the authors tried to promote the functional activity of the pituitary in 5 cases and obtained marked improvement. In 4 cases the attacks virtually ceased; in the fifth, the daily severe attacks were reduced to mild ones 2 or 3 times a week. Four exposures were made at weekly intervals, the administration consisting of cross-fire through the brow and temples, making a total exposure of 12 minutes. Ascoli and Fagioli (*Riforma Medica*, July 10, 1920).

The favorable effect of the X-rays in asthma is due to an action on the liver, resulting in the throwing into the circulation of protein substances insufficient in amount to cause anaphylactic shock but sufficient to desensitize the system in asthma due to hypersensitiveness. K. Hajós (*Zeit f. d. ges. exp. Med.*, xxxviii, 229, 1923).

In 40 cases the writer used the X-rays over the region of the hilum anteriorly and posteriorly on both sides, administering not over  $\frac{1}{2}$  erythema dose over fields of 80 square centimeters through 3 mm. of aluminium. Thirteen cases were cured, 11 much improved, 8 improved, 5 unchanged, and 3 lost sight of. Usually there was increased expectoration for some days after the exposures. In many instances asthmatic attacks ceased after the first treatment. G. Marum (*Strahlenth.*, xvi, 817, 1924).

Four cases in which the asthma was related to exophthalmic goiter. The attacks were brought on by various factors such as temperature changes, coal dust, and especially, emotions or the menses. Skin tests were all negative. Each case was cured of both the Graves's disease and the asthma by **X-ray** exposures of the thyroid. In 1 case, before treatment, administration of a small dose of thyroid gland brought on an attack of asthma; after the treatment, it no longer had this effect. F. Widai and P. Abrami (*Presse méd.*, May 31, 1924)

In 26 cases the writer irradiated the spleen with  $\frac{1}{2}$  the skin dose of penetrating **X-rays**. Of the series 46 per

cent. were cured and 38 per cent. greatly improved. Two were not benefited and 2 abandoned treatment because of a severe attack after the first exposure. In 12 cases the asthma was of 5 to 25 years' standing, yet they were cured by 1 to 3 exposures. M. Gallino and M. Terrada (*Rev. Soc. de med. int.*, June, 1925).

Case of an asthmatic boy of 6 years who was clinically cured by a small dose of **X-ray** over the spleen. Waldbott (*Arch. of Int. Med.*, Nov., 1925).

Small doses of **ultra-violet rays** have been recommended by Duhem for asthma in children.

**Surgical Measures.**—Some cases of asthma are relieved by operative procedures undertaken to correct abnormalities which have been regarded as causing the disorder reflexly. In the nasal cavities the lesions met with in the majority of cases are nasal polypus, deflected septum, and turbinal hypertrophy. The sinuses, including the antrum may also, when diseased, cause asthma. Active measures to remove any of these abnormalities should be instituted whenever found, even though they do not apparently interfere with the physiological functions of the nose.

The association of chronic ethmoiditis and asthma is an intimate one; a deviated septum or a similar lesion within the nose may aggravate the symptoms. Great improvement has followed the **removal of the pathological nasal lesions**. J. Mackenzie Brown (*Annals of Otol., Rhinol. and Laryn.*, June, 1917).

Among 62 patients **operated on** for asthma in the nose and throat clinic, the writers frequently found sinus infections, commonly with polypi or polypoid hypertrophy of the sinus mucous membranes, with little or no free pus. The sinuses most often involved were the ethmoids and antrums. There was pansinusitis in 7 cases. In many cases obstructive deviation of



the septum, hypertrophied turbinate membranes, chronic infection of the tonsils or infected adenoids were found, alone or in combination. When operation is indicated in these cases it should be radical and definitely remove the infection; otherwise, benefit is likely to be transient or *nil*. Bronchitis reduces the operative results. Only 1 patient described himself as "cured" after 3 years; 53 were improved and 9 unimproved. In 14 there was recurrence, sometimes because of return of intranasal pus or polypi. A majority of the cases subjected to asthmogenic tests were non-sensitive; in sensitive cases, specific protein treatment should be given in addition to the operative procedure. C. A. Heatly and S. J. Crowe (Johns Hopk. Hosp. Bull., Dec., 1923).

Where the airway is blocked or there is an obvious focus of infection, **operation** often relieves the symptoms of asthma very much and in young people may even result in a cure, while if the nose is apparently normal the **cautery** may be of great service. Since no specific cure for every case of asthma has been found, every positive method of relieving the symptoms should be given a fair trial. M. C. Tod (Jour. of Laryng. and Otol., Sept., 1925).

Various **nerve resections** for asthma have been undertaken, chiefly by German observers. Kümmel, among others, has performed **removal of the cervical sympathetic ganglia**, with favorable results in 3 cases. Kappis carried out **resection of the right vagus** below the recurrent laryngeal nerve in a number of cases, most of which recovered or improved. Other surgeons, however, have not reported favorable effects, and in a number of instances the operations have led to more or less serious complications.

Case of a man who had been subject throughout life to typical nocturnal attacks. X-ray examination finally showed a mediastinal shadow pushing

the trachea over to the left. Removal of the mass—an intrathoracic adenoma of the thyroid—was followed by cessation of the attacks. J. R. Charles (Bristol Med.-Chir. Jour., lxii, 73, 1925).

**Intralaryngeal injections** for the purpose of reducing the catarrhal process of the bronchial mucous membrane have been followed by satisfactory results.

The quantity of the solution injected and the amount of the agents contained in each injection must, of course, be adjusted to the patient's age and condition. Bowie, referring to the solutions described below, states that 1 dram (4 Gm.) will be sufficient for a child from 5 to 10 years of age, 2 drams (8 Gm.) from 10 to 15; after this, from 3 to 5 drams (12 to 20 Gm.) will suffice at each sitting.

First solution: a 5, 10, 15, or 20 per cent. solution of **menthol in almond oil**.

Second solution: 2 to 5 minims (0.12 to 0.3 c.c.) of a 2½ per cent. solution of pure **crystals of iodine in almond oil** added to each dram of the first solution.

Third solution: 5 minims (0.3 c.c.) of a 10 per cent. solution of **oil of hops in almond oil** added to each dram of the first.

In **Ephraim's endobronchial method** of treatment, the spraying is done into the bronchi themselves. The instruments consist of a rubber tube with equidistant markings and a special conical and slightly bent spraying tip. The other end of the tube is connected with a 15-c.c. (½ ounce) receptacle in which are placed the solutions to be introduced. Joined to this system is a tube from a compressed oxygen tank, with safety valve blowing off at 1 kilogram pressure. The larynx is first anesthetized with **alypin-epinephrin solution**, next the upper trachea, and the larynx again with **alypin-**

epinephrin or cocaine spray, and then the lower trachea and roots of the bronchi with a 1 per cent. spray of quinine and urea hydrochloride and epinephrin solution.

**Intratracheal treatment** of asthma was tried by the writer in 15 cases and 7 may be regarded as cured, no attacks having returned during about a year to date. Six were much improved but still have an occasional attack and return for further treatment. The attacks are rare, however, and much milder. De Levie (Nederl. Tijds. v. Gen., Jan. 26, 1918).

**Bronchoscopic treatment** of asthma has been carried out with favorable results in Chevalier Jackson's clinic.

An **autogenous vaccine** is made from material obtained at the 1st bronchoscopy; then a medicated solution is instilled into the right and left main stem bronchi in succession. This solution usually consists of: **Adrenalin** (1:1000), 20 drops; **cocaine** (10 per cent.), 10 drops; normal saline solution, 1 dram (4 c.c.). Any thick, clinging mucus is removed by suction or swabbing before the instillation. Three treatments are given at weekly intervals, then at longer intervals on recurrence of asthma. Passive congestion of the mucosa has generally disappeared by the third treatment. Eight out of 16 cases showed marked improvement. W. F. Moore and R. M. Lukens (Atlantic Med. Jour., Sept., 1924).

**Bronchoscopy** alone, affording a means of cleansing the overloaded mucous membrane, temporarily alleviates the symptoms and yields relatively permanent results in many cases. At the first bronchoscopy morphine is usually given. In adults a 10 per cent. solution of cocaine is applied deep enough in the pharynx to inhibit the superior laryngeal nerve. Bronchoscopy is not contraindicated during a bronchial asthmatic attack. The mucous membranes are cleared either by sponging or by aspiration, after which 5 c.c. (80 minims) of cocaine-adrenalin solution are generally instilled in

each main bronchus. The bacteriologic studies showed that *Streptococcus viridans*, *S. hemolyticus* or a hemolytic strain of *S. aureus*, in pure culture or associated, are present in nearly all cases. These organisms show a marked attenuation, which may account for the non-occurrence of metastatic infection but does not render vaccines prepared from them less potent. Twenty-seven cases studied are divided into a group with bronchoscopically evident active suppurative tracheobronchitis, nearly all of which were definitely improved by bronchoscopic treatment, and 7 with chronic passive congestion, showing either a bluish-red, leathery appearance of the mucosa with little or no secretion, or inspiratory or expiratory collapse of the bronchi, likewise with little secretion; in the latter division relief was temporary or absent. W. F. Moore (Amer. Jour. Med. Sci., June, 1925).

**Psychotherapy** has seemed serviceable in the hands of some observers.

Psychoanalysis is usually most successfully carried out in connection with an attack, when the patient's mind is concentrated on his condition. The circumstances attending the patient's first attack frequently yield a clue for the institution of psychotherapy. In 7 cases psychoanalysis cured asthma after all other measures had failed. Only in 2 cases was a sexual factor clearly present. Moos (Munch. med. Woch., June 22, 1923).

**Climate** has been thought to exert a considerable influence upon the explosion of asthmatic paroxysms. Observation indicates, however, that few cases are permanently cured by a change of residence, while practically all are momentarily benefited by any change they may make. Where the paroxysms are greatly under the influence of bronchial catarrh, the removal from a cold and damp climate to a warm and dry one may prove of lasting benefit. In seeking

for a climate it is well to remember that, as stated by Brügellmann, for a time immunity from attacks may be apparent, but finally the symptoms are apt to reappear. F. I. Knight reported the case of a physician who changed his residence and practice several times during his life, on account of asthma, and who finally got relief by going back to the place from which he started. Tucson, Arizona, and Colorado in the United States, Mont-Dore-les-Bains in France, the Engadine in Switzerland, and Bournemouth in England are well spoken of in this connection.

Of 7 patients who reacted in a negative manner to the various cutaneous tests, 4 were sent to a **warm climate**; all were benefited and 2 were definitely relieved. Lambright (Ohio State Med. Jour., Apr., 1922).

For asthmatic subjects living in the lowlands and exposed constantly to substances productive of asthma, the writers recommend a stay in the **mountains**, where the air is free of such substances and a marked bronchitis, if present, may be recovered from. If the results are to be maintained upon return to the lower level, however, **hyposensitization** should be carried out while the patient is still in the mountains, if not with a known atopen, then with a general antiallergen such as **tuberculin**. Van Leeuwen, Varekamp and Bien (Klin. Woch., Mar. 25, 1924).

CHARLES E. DE M. SAJOUS,  
Philadelphia.

**ASTIGMATISM.**—This term, proposed by Dr. Whewell, has been adopted, with slight modification, in all modern languages. The shorter form *astigmia* is coming more into general use.

**DEFINITION.**—That error of refraction by reason of which rays, coming from a single point and pass-

ing through the refractive surfaces of the eye, are not turned toward a single point, and, therefore, cannot be perfectly focused on the retina. The word astigmatism is often used alone to denote regular astigmatism.

### IRREGULAR ASTIGMATISM.

**DEFINITION.**—The form of astigmatism arising from irregularity of a refractive surface or of the refractive index of the cornea or lens, so that rays passing through different parts of these surfaces are turned in various directions and can never be brought to a perfect focus.

Out of 1000 eyes examined by the writer the absolute astigmatism and the corneal astigmatism were the same in 475 cases—that is, 47.5 per cent.; 230 were hypermetropic astigmatism, 89 were myopic, 190 showed compound myopic astigmatism, and 138 mixed astigmatism. J. Rowan (Brit. Med. Jour., Jan. 13, 1912).

**SYMPTOMS.**—There is imperfect vision, the blurring being proportioned to the degree of the defect and the size of the pupil, and affecting the seeing at all distances and all times. An eye subject to this defect is permanently "weak," cannot attempt work requiring very accurate seeing, and is liable to be strained in reading, sewing, etc. The irregularity of surface is generally accompanied by more or less haziness or opacity. This may be the opacity remaining in the cornea when irregular astigmatism has been caused by corneal inflammation, or it may be an opacity of the lens, when such astigmatism is the forerunner of cataract.

Pronounced irregular astigmatism causes *monocular diplopia*, or *polyopia*. A lamp-flame or the moon at night is

seen multiplied, the different images of it usually overlapping each other more or less. It also shows itself by the distortion of letters, and in the appearance of additional lines about or upon them, plain type being made to appear like fancy type. The "rays" which appear to proceed from a point of bright light, as a star or a distant electric lamp, are due to irregular astigmatism. An eye free from astigmatism would see a star as a mere point of light.

**ETIOLOGY.**—Some irregular astigmatism is present in all normal eyes. When it causes no impairment of vision, below the usual standard of 20-xx, it is called normal. Normal irregular astigmatism is generally caused by the inequality of curvature in the periphery of the dilated pupil, this being cut off when the pupil contracts.

Irregular astigmatism may be due to changes in the lens preceding cataract or to irregularity of the surface of the cornea, as from abrasion or superficial ulceration.

General bulging of the cornea is commonly not uniform and gives rise to irregular astigmatism, the common form being conical cornea; but the most common cause is incomplete restoration of the corneal tissue to normal after keratitis. Peripheral groove formation and consequent bulging of the cornea cause irregular astigmatism of high degree.

Does pterygium cause astigmatism? The prevailing theory seems to be that a pterygium begins at the corneal edge by reason of the presence of a minute abrasion or ulcer of the cornea which, in healing, draws into itself a small fold of adjacent conjunctiva. This makes traction on the latter membrane and starts the growth.

A little later other abrasions, from one cause or another, occur near the head of the growth on the cornea, and in healing the head advances still nearer the pupil, becomes large, and the body of the growth becomes wider, thicker, and more vascular, finally developing more or less connective tissue. The unattached wings of the growth furnish a fine culture bed for bacteria, and slight corneal abrasions may easily become infected. This membrane, as a whole, it can readily be conceived, is quite capable of making a smart traction on the cornea, quite enough to alter decidedly the relative length of the two principal meridians. Illustrative personal case which demonstrates that a pterygium can and does produce astigmatism. Hall (Texas State Jour. of Med., Oct., 1911).

In private cases under observation from 2 to 17 years, the writer found that the axis of the correcting lens in hypermetropia tends with age to rotate from the vertical toward the horizontal, and in the opposite direction in myopia. In nearly every case the rotation was in accord with a suggested law that the cylinder axis tends to rotate toward a point which might be called the position of rest. The axial changes were always gradual. The average rotation in 39 cases in an average period of 6.4 years was for the right eye  $17^\circ$  and for the left eye  $19^\circ$ , and the average annual rotation thus  $2.7^\circ$  for the right and  $3^\circ$  for the left. A study of the cases by decades showed the rotation to have begun as follows: In the 1st decade of life, no case; 2d, 1; 3d, 3; 4th, 6; 5th, 16, and 6th decade, 13. Of the 78 eyes, 60 had slightly altered in other respects, 34 changes affecting spheres alone, 13 cylinders alone, and 13 both spheres and cylinders. The strength of cylinders was decreased in 6 and increased in the others. A. W. Stirling (Arch. of Ophth., Jan., 1923).

**TREATMENT.**—With irregular astigmatism following keratitis there is always, at first, haziness of the cornea; and probably, remedies for corneal

opacity improve vision partly by lessening irregular astigmatism.

In a few cases **dilatation of the pupil** may improve vision by admitting light through a better portion of the cornea or crystalline lens. **Iridectomy** is applicable in some cases for the same purpose. Contraction of the pupil often makes vision better by lessening the areas of diffusion. Solutions of **pilocarpine**, 1:500, or **eserine**, 1:2000, may be instilled for this purpose. Stenopaic spectacles improve vision, but interfere too much with the field of vision to be of much practical value; a horizontal slit is the most practical of stenopaic apparatus. For the mass of cases the correction of regular astigmatism commonly associated with the irregular, and the use of **spherical lenses** that will prevent the straining of accommodation, is the only available optical treatment.

### REGULAR ASTIGMATISM.

**DEFINITION.**—It is the astigmatism that can be corrected by a cylindrical lens.

**SYMPTOMS.**—It causes the blurring of some or all lines looked at. The eye is able to see with perfect clearness only the lines running in one direction at any one time, although by changing its accommodation it may be able to see clearly lines running at right angles to the first. These two directions, in which lines may be seen clearly, the "principal meridians," may be perceived by the patient, although usually they are only recognized when the eyes are carefully tested. A certain adjustment of the power of accommodation renders lines equally blurred in all directions. Astigmatism may thus cause imperfect vision; but very often the imperfection is only slight and has never been noticed

by the patient. Generally there is some eye-strain, from the effort to focus clearly the lines running in different directions, which all objects present, or to recognize from imperfect retinal images the real form of an object. The symptoms complained of are weakness of the eyes, headache, pain in the eyes on use, inability to use them long, excessive lachrymation, photophobia, nervousness, twitching of the eyelids, and even more serious nerve disease.

Astigmatism usually coexists with hyperopia and myopia, and a portion of the symptoms may be due to one of these. The eye-strain caused by astigmatism is probably a very important factor in the development of myopia.

Many observers believe that astigmatism against the rule, or astigmatism with the meridians placed obliquely, causes more annoyance than astigmatism of the usual form, in which the meridian of greatest refraction is vertical. This latter may be due to the fact that the astigmatic eye can see perfectly only the lines that run in the direction of one of its principal meridians, and that most of the lines which we wish to distinguish are either vertical or horizontal.

Uncorrected astigmatism has been regarded as interfering with the use of various optical instruments. With the microscope only the uses of comparatively low powers are interfered with.

**ETIOLOGY.**—Astigmatism is caused by a lack of symmetry in the curvature of the refracting surfaces of the cornea or crystalline lens, or an oblique position of such surfaces with reference to the visual line. It does not depend on distortion of the retina. Astigmatism caused by the cornea may be partly or wholly corrected by an opposite astigmatism caused by the

crystalline lens. The wide use of the keratometer (ophthalmometer) of Javal has furnished extended statistics regarding corneal astigmatism, which, by comparison with the total astigmatism of the eye, also indicates the astigmatism due to the crystalline lens.

Extensive wounds or incisions of the cornea give rise to permanent change in the corneal curvature and astigmatism. This is most noticeable after cataract extraction. The astigmatism is highest a few days after the corneal wound has closed, and from then on slowly diminishes until usually within three months, but sometimes later, it becomes stationary. The changes of corneal curvature are flattening of the cornea at right angles to the incision, and increased curvature in the direction of the line joining the ends of the incision.

**DIAGNOSIS.**—Astigmatism is detected and measured by all of the various methods of determining the refraction of the eye, and should be sought by more than one method in any given case. The chief reliance is to be placed on the keratometer (ophthalmometer), skiascopy, and the test-lenses. Whether it is sometimes corrected by unequal contraction of different parts of the ciliary muscle or is not so corrected, must still be regarded as uncertain.

**TREATMENT.**—For regular astigmatism the usual remedy is the wearing of **cylindrical lenses**, which should correct the full amount of the astigmatism and should be worn constantly. Any case of astigmatism may be thus corrected by a convex cylindrical lens with its axis placed parallel to the meridian of greatest curvature, or by a concave cylindrical lens with its axis placed perpendicu-

lar to this, or by two lenses of proper strengths with their axes respectively parallel to the two meridians. As may readily be demonstrated mathematically or by trial, the optical effect of any possible combination of cylindrical lenses may be produced by the proper single cylindrical lens combined with the proper spherical lens. By looking obliquely through a spherical lens, a spherocylindrical effect may be obtained, and patients sometimes resort to this when the glasses worn do not fully correct their astigmatism.

The fact that **corneal incisions** change the corneal curvature has suggested their employment for the correction of astigmatism, and where an operation is necessary the corneal incisions may be so planned as to influence favorably the existing astigmatism. The **galvanocautery** has also been suggested for this purpose.

EDWARD JACKSON,  
Denver.

**ATHETOSIS.—DEFINITION.**  
—Athetosis (*âthēros*, without fixed position) or athetoid movements should be classed as a cerebral affection characterized by slow, deliberate, purposeless, involuntary, more or less rhythmic, and exaggerated movements which are chiefly confined to the hands and feet of one or both sides.

[Although previously observed by Heine and Johannes Mueller in their studies on associated movements, this peculiarly interesting condition was first described, in 1871, by Hammond. A few years later it was studied at greater length, particularly by Clay-Shaw, in England, and Oulmont, in France, and it is to the last-mentioned authors that we really owe our present clear conception of this interesting set of pathological movements. Since then important contributions have been made by Charcot and his followers, Dejerine, Sollier, Arn-

spurger, Audry, Oppenheim, von Monakow, and more recently Lewandowsky. COLLINS AND ZABRISKIE.]

Athetosis occurs usually as a sequela of infantile hemiplegia, although not limited to it exclusively, for even Hammond described 4 cases in which there was no hemiplegia apparent. It has also been observed in epilepsy, idiocy, tabes, and paresis. These are the exceptions, however, and its occurrence, especially in tabetics and idiots, should be accepted with more or less reserve.

We see this condition most often in infantile hemiplegia, as we have said. It is not confined exclusively to this period of life, however, but sometimes, though rarely, develops in adults. While this adult form seems to have been fairly well established, there are some authors (Marie) who insist that it is extremely rare and often confused with hysteric athetoid movements. Lewandowsky also found its appearance in adults to be exceptional, having seen only one case among several hundred hemiplegics. He considers it "an almost specific symptom of hemiplegia acquired in early life."

The muscular movements occur as slow, deliberate, tortuous movements of the hands and feet involving usually the arm as well. They are almost always more pronounced in the arms and hands than in the lower extremities. They are purposeless in character, more or less exaggerated and rhythmic, and, as in chorea, quite involuntary, so that there is a decided inability to maintain the extremities in any given posture. They occur during sleep and are exaggerated by emotional disturbances.

The movements consist usually of flexion of the wrist, with hyperextension of the fingers at the metacarpophalangeal joints. The distal phalanges

are often flexed and the thumb either abducted and extended or adducted and extended. This is the characteristic position of the hand assumed on extension of the arms; that of the foot is a position of equinovarus with the great toe extended. This attitude, which is really the result of an unequal tonus, *i.e.*, an ill-balanced innervation of protagonists and antagonists, cannot be maintained for even a limited period of time, and there ensues the remarkably peculiar muscular activity so characteristic of the condition. A gradual relaxation of the stiff, rigid muscles takes place and a flaccid state appears, or the hand may slowly extend, the arm supinate, and the fingers bend and flex. There is often slow pronation or supination with a moderate rotation of the whole arm. Sometimes there is a slow, deliberate flexion of the first metacarpophalangeal joint, followed by the others in slow succession, the first joint gradually regaining its original posture.

It can readily be seen how many different combinations of movements are possible, and the difficulty of adequately describing them. Once seen, however, they are never forgotten, and the similarity to the moving arms of a polypus to which von Monakow has called attention will be appreciated.

A certain rhythmic quality which becomes apparent if these cases are closely watched is very characteristic. It is marked by pauses of variable duration between the spasmodic muscular contraction, during which the musculature of the affected limbs may be quite flaccid, of normal tonus, or in case of a well-established hemiplegia moderately spastic. This is known as the period of latency.

The effect of exaggerated joint ex-

cursions so striking in many of these cases is produced by lack of proper balance between the protagonists and antagonists. During flexion of the hand, for instance, the extensors are unduly relaxed, whereas in extension of the fingers the flexors release their hold. That it is due to this rather than a mere overactivity of the protagonists is apparently demonstrated by the unequal disturbance of flexion and extension of the different phalanges. On the other hand, if we were dealing with a permanent contracture, the flexion would be more evenly distributed.

In many instances, during the interval between the spasmodic movements, instead of muscular relaxation, there is a definite, constant muscular contraction, fixing the component parts of the extremity in a firmly set position, which is maintained for the same time as the relaxation pauses. This is really a tonic spasm of the muscles, which is known as "*spasmus mobilis*" of the English authors, and manifests itself as the well-known position of flexion of the hand with extension of the fingers so often figured in the textbooks. It is often a very powerful contraction resisting absolutely all voluntary effort on the part of the patient to overcome it, and it can be overcome passively only after a considerable effort. The end of the spasm comes as a relaxation of the tonically contracted muscles, to be followed immediately by the slow, deliberate athetoid movements. This relaxation occurs sometimes rapidly, sometimes slowly, but it almost invariably constitutes the termination of a spasm. The mobile spasm is one of the most constant features of athetosis, in our experience as well as

others (Lewandowsky, Oulmont), and, although it does not occur at every pause, nearly every patient intelligent enough to give correct answers will tell of its appearance at different times. The muscles of the arm and forearm may be the seat of a powerful spasmodic contraction, while the fingers exhibit typical athetoid movements. This latter is often difficult to differentiate from a true hemiplegic contracture, on account of its extreme rigidity and resistance to passive movement. Lewandowsky has called attention to the fact that a true contraction can never be overcome by voluntary innervation to the antagonists because of the blocking of impulses according to Sherrington's theory. The mobile spasm, however, sometimes can be overcome by repeated voluntary effort, since there is no true arrestation of impulses.

The mental state of these patients depends upon the severity of the causative lesion and has nothing to do with the athetoid state itself. It may be complete idiocy, on the one hand, or a perfectly normal mentality, on the other. In other words, the same varied mental state one finds in hemiplegia.

More recently, interest has again been aroused in that form of athetosis to which the name "*athétose double*" has been given by the French writers.

There seems little doubt now that it is a condition quite apart from the posthemiplegic variety and is not merely a bilateral form of the latter. It is of extremely rare occurrence, but possesses several distinguishing features which allow a fairly definite separation from the bilateral form. The condition is almost invariably



associated with other congenital defects, with or without bad heredity, and it is usually acquired in early infancy. There is nearly always some degree of defective intellect, however slight it may be, as well as speech defect varying from a simple dysarthria and aphasia to complete anarthria (Oppenheim). Spastic diplegia is frequently associated with it, although cases have been reported in which there were no spastic phenomena whatever. The chief characteristics of double, or idiopathic, athetosis are: the general distribution of the movements, the face always involved and more so than the feet, the disappearance of the movements during sleep, the combination with associated movements, mobile spasm, and the remarkable manner in which they are increased during excitement or when the attention is directed toward them.

The movements of the face are perhaps the most characteristic of them all. The lips retract slowly, accompanied by wrinkling of the forehead; the eyes are wide open or closed, imparting to the facial expression a peculiar grimacing stare. The features slowly compose themselves and again the same muscular play takes place, now limited to one side of the face, now the other. The head and neck undergo peculiar twisting, rotary movements which often spread over the trunk. The hands, arms, and legs assume the fixed position characteristic of the hemiplegic type, and remarkable postural effects ensue, reminding one greatly of Huntington's chorea. There are long quiescent periods when the patient is not excited or aroused emotionally, but the movements are always brought into

play whenever he becomes interested or excited or his attention is directed toward them. The gait, if walking is possible, is characteristic because it almost always brings the entire combination of athetoid movements into play. Walking often provokes mobile spasm in the lower extremities, sometimes to such an extent as to render more than a few steps impossible without support.

[A peculiar flexor spasm of the spine, tending to throw these patients forward and seriously disturb their equilibrium, is rather frequent also. The latter condition was so marked in a little girl of 9 years, recently observed, that she could not walk at all unless supported under the shoulders. This could not have been due merely to a profound degree of spasticity, because when supported as above the patient walked—a fairly normal manner; furthermore, when in the recumbent posture the legs showed an amount of spasm so mild that it could in no way account for the gait without support. Haupt (D. Arch. f. Nervenheilk., 1907, No. 33) has also called attention to this fact, although he does not attempt to explain it. COLLINS AND ZABRISKIE.]

**PATHOLOGY.**—A glance through the literature on athetosis demonstrates very clearly that there is no particular focal lesion which will produce athetoid movements. Von Monakow has collected about one hundred published cases with autopsy, in which the lack of unanimity of findings is very striking. In about 60 per cent. the lesion was situated in the region of the posterior limb of the internal capsule, *i.e.*, postthalamie region adjoining section of the lenticular nucleus, the optic thalamus, and the retrolenticular region. Lesions have also been found in the corona radiata, tegmentum, in the vicinity of the red nucleus, the cerebellar hemisphere, the dentate nucleus, and the

peduncles with the substantia nigra. In some instances no lesion at all was found. It seems, however, fairly well established that destructive lesions do not produce this condition, but disturbance somewhere in the pyramidal tracts.

Athetosis and chorea are exteriorized *via* the corticospinal paths, but behind their appearance is an afferent disorder of regulation, attributable to lesions situated on the cerebello-mesencephalo-thalamo-cortical path. In consequence, "voluntary" movements *via* the corticospinal tracts exhibit characters corresponding to the functional defects; these tracts are also being usurped by "spontaneous" movements of choreiform or athetoid character. S. A. K. Wilson (Lancet, Aug. 1, 1925).

**DIAGNOSIS.**—Oulmont, in his excellent description of athetosis (*Thèse de Paris*, 1878), insisted upon four distinctive features which characterize the condition: 1, the slow, deliberate quality of the movements; 2, the exaggeration; 3, limitation to the hand and foot; 4, transformation into a mobile spasm. We are rather in accord with Lewandowsky, who takes exception to at least two of these in regard to their diagnostic significance. Many authors have described cases in which the athetoid movements were of extremely mild type and only to be seen after careful observation. These movements are also not strictly limited to the hands and feet, for we have observed a slow sinuous twisting of the face in one case and Lewandowsky has twice observed them in the shoulder. Von Monakow also mentions face involvement.

The diagnosis of athetosis is usually not difficult if we bear in mind its distinguishing features, *i.e.*, the slow, rhythmic character of the

movements and the mobile spasm. These two characteristics are absolutely necessary for the diagnosis of athetosis, and they constitute the principal points of differentiation from chorea (whether it be post-hemiplegic, Sydenham's or Huntingdon's), from posthemiplegic associated movements, or from other similar forms. The condition with which athetosis is most frequently confused is posthemiplegic chorea. In the latter the sudden jerky manner in which they begin, the snake-like, twisting character of the movements themselves, their aimlessness, the complete flaccidity during the pauses, and the absence of mobile spasm serve to differentiate it from the former in every instance. Huntingdon's chorea is sometimes mistaken for double athetosis or *vice versa*. But here, again, the absence of all spastic phenomena, the time of life at which it begins, the family history, and mental trouble appearing late in life are characteristic of the former.

The four distinguishing points given by Oulmont in his above-mentioned thesis should really apply only to the hemiplegic form and not at all to the double form, since in the latter only the first and fourth of these distinctive features, *viz.*, the slow, deliberate quality of the movements and the transformation into a mobile spasm, are true.

JOSEPH COLLINS

AND

E. G. ZABRISKIE,

New York.

**ATHREPSIA.**—In its milder forms, this condition of infants is also frequently known as **malnutrition**; in its more severe forms, as **marasmus**, **decomposition**, or **infantile atrophy**.

**SYMPTOMS.**—The general clinical picture is that of wasting of the infant's body, associated with an apparent inability to assimilate food. The condition may have arisen gradually, as a result of repeated minor disturbances, or rapidly, in particular where diarrhea is a prominent accompaniment. Increased feeding may bring on diarrhea, while an attempt to correct diarrhea by cutting down the intake of food may result in fatal inanition. There is a negative nitrogen and mineral salt balance. Acidosis occasionally coexists.

The changes in general appearance may be summarized in the expression of an "excessively thin, wrinkled old man." In the cases running a rapid course, 1 to 3 ounces of weight may be lost daily. At first there is irritability, crying and great hunger; later, an ominous state of apathy and weakness. Vomiting is common.

Often the pulse is small and slow, the breathing rapid and later irregular. The temperature is irregular and subnormal (96° to 98° F.). Anemia is present. The infant sleeps poorly. In advanced cases the "hunger stool" is frequently in evidence—dark, small, and with much mucus. The urine may show albumin, and generally exhibits a rise in the ammonia coefficient.

Advanced symptoms are edema, cyanosis, purpura, and sudden attacks of collapse, which may be fatal. There is great susceptibility to grave infectious complications. In cases previously free of diarrhea, the advent of this complication may rapidly close the scene.

#### ETIOLOGY AND PATHOGENESIS.

—The history of athreptic infants often elicits improper feeding or some form of gastrointestinal or other infection which has been followed by impairment of nutrition. The condition is common in premature infants and infants with congenital disease of the heart, lungs, alimentary tract or brain.

All the factors which lead to diarrhea disturbances, anhydremia and intoxication may also be causative factors of athrepsia (Hess). The essential feature of the condition has been held to be an inability to assimilate, of unknown origin. Marantic infants may fail to gain in weight even in the absence of clinical evidence of gastroenteric disorder. Even in severe cases, it

is rarely possible to demonstrate a pathologic condition of the intestinal glands, which some had assumed to be the cause of the disability.

Among the dietetic errors which may precede athrepsia are an ill-balanced diet, containing, *e.g.*, an excess of carbohydrates, particularly in the form of cereal waters, gruels, or condensed milk; likewise, insufficient feeding, as when mammary secretion is deficient or inadequate artificial mixtures are given. A deficiency of vitamins in the food has also been incriminated.

In athrepsia there is loss of the adipose tissue, autophagia of the body protein, and a chronic loss of water and mineral substances. Sudden fluctuations of weight are ascribed mainly to variations in the content of water and salts. Loss of alkali salts is held to be promoted through the improper disposition of the sugar and fats in the intestine, which not only excites diarrhea by irritation but calls for alkali to neutralize the excess of acids formed in the bowel. The body cells at large are thus eventually weakened in salt content. Acidosis, when present, may be ascribed to reduced blood flow through the tissues and to the partial starvation. Nearly always, in severe marasmus, there is a *hypoglycemia*, the blood sugar falling at times below  $\frac{1}{2}$  the normal.

Marriott, mindful of the circumstance that, to bring cow's milk to the optimum acidity of pH 3.75 for rennin action, 3 times as much HCl is required as in the case of breast milk, has ascribed some cases of malnutrition to this relatively high "buffer value" of cow's milk, which requires a greatly increased secretion of HCl in the infant's stomach to deal properly with the milk as well as to avoid a tendency to bacterial invasion of the duodenum. To be sure, athrepsia can occur in the breast-fed, but the severe forms of it are rare unless intercurrent disease has existed.

**DIAGNOSIS.**—Athrepsia is indicated if loss of weight and diarrhea occur when the food-intake is somewhat augmented. From simple dyspepsia, which requires different treatment, it is differentiated by the history of loss of weight, recurring diarrhea, and sometimes febrile infections. A distinction has also been made between athrepsia and simple inanition, due to inadequate feeding but without failure of assimilatory function.

Again, it should be borne in mind that loss of weight may be due to syphilis, tuberculosis or other causes of cachexia.

**PROGNOSIS.**—Recovery appears to be impossible where as much as or more than one-third of the body weight has been lost. Otherwise, recovery may often be obtained by proper treatment, even in severe cases. The prognosis is improved by the ability to obtain breast milk for the infant and to exclude exposure to sources of infection. The older the infant, the better the outlook. Convalescence may take several months.

**TREATMENT.**—In athrepsia there is an obvious indication for liberal feeding. According to Marriott, few infants whose weight is as low as  $\frac{1}{2}$  the normal for their age gain on less than 160 calories per kilo., and many require 200 calories or more. A shift should, if at all possible, be made to feeding with human milk. Hess advises only a moderate quantity at first, best insured by drawing off the milk before feeding, as these infants drink too rapidly. About 200 to 300 c.c. (7 to 10 ounces) daily suffices to sustain the infant temporarily. Seven to 10 feedings of 20 to 30 c.c. each may be given, with weak tea or water allowed *ad lib.* between feedings. The daily total should be increased as rapidly as possible, so that not later than after 7 to 10 days about 100 calories (130 to 150 c.c.) per kilo. are being given. Later, direct breast feeding can be instituted. In spite of adequate feeding, a shorter or longer period of stationary weight should occasion no surprise. The intake should be steadily increased as long as there are no gastrointestinal disturbances. If the quantity of breast milk is inadequate, cane and milk sugar, corn syrup or dried milk may be cautiously added to it. Later, 100 c.c. of boiled butter-milk or skim milk, which is rich in salts and proteins, may be given daily. The total amount of fluid ingested, including plain water, should equal approximately one-fifth of the infant's body weight daily (Hess).

Where breast milk is unobtainable, artificial mixtures will have to be resorted to. According to Marriott, cow's milk, if acidified with lactic acid and enriched with corn syrup, is readily digested, *e.g.*, 22 ounces of whole lactic acid milk with  $1\frac{1}{2}$  to 2 $\frac{1}{2}$  ounces of syrup. In infants who fail to gain even on such a mixture, he strongly recommends re-

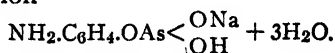
peated transfusions of matched citrated blood—about 1 ounce for 3 pounds of body weight. Often the infant will then begin to gain, without any change in the feeding. Another measure is dextrose intravenously, given slowly in a 20 per cent. solution— $\frac{1}{3}$  to  $\frac{1}{2}$  ounce per pound of body weight. Glucose thus given is only partly utilized; but if insulin is given at the same time, there is better utilization, and a gain in weight results. A 20 per cent. glucose solution containing 15 units of insulin per 100 c.c. has enough glucose to "buffer" completely the insulin—an essential feature if serious consequences from hypoglycemia are to be avoided. A gain in weight almost invariably occurs, even in infants with infections. The gain is not later lost when the injections are discontinued. This measure is reserved for the extreme cases, and may be used daily.

Albumin (protein) milk has also been much used, permitting of rapid increase of feeding without promoting fermentation, but has a caloric value of only about 12 to the ounce. The initial amount is 200 to 300 c.c. daily, later rapidly increased with addition of carbohydrates.

Rohmer recognizes an acute form of athrepsia which corresponds to Finkelstein's "decomposition" and is featured by diarrhea with rapid, continuous loss of weight. He recommends feeding with skimmed breast milk in quantities twice those usually taken of normal breast milk. A return to the normal breast milk can generally be made at the start of the 2d week.

Other important measures in athrepsia comprise a sufficient amount of external heat where there is hypothermia, the pushing of fluids by various routes where there is dehydration, orange juice, codliver oil, and stimulants for attacks of collapse. In the latter condition Hess recommends epinephrin intramuscularly, 3 to 5 minims (0.2 to 0.3 c.c.). Hallez has advocated tri-weekly subcutaneous injections under the abdominal skin of 4 c.c. (1 dram) of sterilized breast milk. S.

**ATOXYL, or SODIUM ARS-ANILATE**, is an organic compound of arsenic having the chemical composition



It may be said to consist of acid sodium arsenate in which one hydroxyl group has been replaced by aniline ( $C_6H_5.NH_2$ ). It occurs as a white, crystalline, odorless powder, having a slightly saline taste. It is soluble in 6 parts of water and in approximately 125 parts of alcohol; when left standing a solution of atoxyl in water becomes yellowish. The substance contains about 26 per cent. of elemental arsenic. **Soamin** is a preparation of sodium arsanilate embodying 5 molecules of water of crystallization to each molecule of the arsenic compound. It contains about 22 per cent. of arsenic.

**DOSE AND MODES OF ADMINISTRATION.**—Atoxyl should be used exclusively by hypodermic injection, as when taken orally it is broken down by the hydrochloric acid of the gastric juice. Its dose is  $\frac{1}{3}$  to 3 grains (0.021 to 0.2 Gm.) injected on alternate days and gradually increased if required.

**PHYSIOLOGICAL ACTION.**—The action of atoxyl is in many respects that of arsenic, slowed down through the fact that decomposition products are set free only gradually from the original organic combination. Atoxyl, while quickly absorbed, is said to be less promptly taken up by the tissues than are the inorganic preparations of arsenic. Its very pronounced effect on the parasites of trypanosomiasis ("sleeping sickness") is thought by many to be due, not to the compound itself, but to organic decomposition products formed from it in the system. Arsanilic acid itself is almost non-toxic to trypanosomes. The greater part of the amount of atoxyl introduced is quite rapidly excreted in the urine, but

only a small proportion as inorganic arsenic. Upon continuous administration, excretion of the drug is less rapid and there results a slight cumulative tendency.

**UNTOWARD EFFECTS AND POISONING.**—The symptoms arising from toxic doses of atoxyl consist of dizziness, headache, tinnitus, deafness, disturbances of sight, vomiting and diarrhea, fever, colic, albuminuria, and partial paralysis of the lower extremities. By far the most important of these possible effects is that on the eyes. So many cases of blindness, usually permanent, have occurred during the use of atoxyl, even in moderate doses for therapeutic purposes, that the drug can by no means be considered a harmless substitute for inorganic arsenic, as some of its sponsors would have had us believe. Thus, Koch in 1902 reported 1633 cases of sleeping sickness treated with atoxyl, with 23 cases of blindness as a result. Schrimmer reported a case of optic atrophy in a patient who had received 52 biweekly injections of atoxyl, amounting altogether to 9.9 grams.

Case of almost complete blindness from 1.2 Gm. (18 grains) of atoxyl given over a period of 26 days, for a severe anemia. A study of atoxyl amblyopia led the author to conclude that the toxic action of atoxyl on the eye cannot be excluded even by the cautious therapeutic employment of the drug. It is especially to be feared when there is latent or obvious disease of the central nervous system, cachexias, autointoxications, chronic infections of the nervous system (lues, etc.), and intoxications, especially chronic alcoholism. These should preclude the use of atoxyl. R. Steinebach (Berl. klin. Woch., June 15, 1914).

The lesion caused by atoxyl where blindness results from its use is an atrophy of the optic nerve,—a phenomenon only very rarely induced by intoxication with inorganic forms of arsenic. Moderation in dosage does not seem to preclude the occurrence of visual disorder, as, while some patients have withstood enormous amounts of atoxyl, atrophy has followed the administration of eight 0.1-gram doses. Ophthalmoscopically there are at first to be seen fine vitreous opacities and narrowing of the arteries; the subsequent progress to complete atrophy may occupy a few weeks to a year or more (McAlester). Examination *post mortem* by Nonne of the optic pathways of a cancer patient treated with atoxyl, blindness resulting, showed parenchymatous degenerative processes in the portion of the optic nerve next to the chiasm as well as in the chiasm itself.

Examination of samples of pure atoxyl kept 3 or 4 years in a tropical locality showed that it is liable to spontaneous decomposition into highly toxic substances. The decomposition was complete in the samples examined; every 0.5 Gm. ( $7\frac{1}{2}$  grains) of atoxyl—a dose commonly given to trypanosomiasis—was changed into 0.03 Gm. ( $\frac{1}{2}$  grain) of arsenous anhydride and 0.56 Gm. ( $8\frac{3}{4}$  grains) of sodium arsenate. Atoxyl should be examined in the locality where it is to be employed and analyzed before clinical use. François (Bull. de l'Acad. de Méd., Mar. 19, 1918).

The toxic effects observed from use of atoxyl in animals include ataxia and tremors, particularly in the cat, and renal hemorrhages in the dog. Birch-Hirschfeld and Igerheimer observed in dogs and rabbits which had received small doses of atoxyl for

some time destructive processes in the optic nerve, retina, and spinal cord, together with paresis of the bladder and rectum.

**THERAPEUTIC USES.**—In trypanosomiasis atoxyl has yielded pronounced beneficial results. Koch, as already mentioned, using it in a large number of cases, found no other preparation of arsenic that gave equal results. He injected 0.5 Gm. ( $7\frac{1}{2}$  grains) on two successive days, then allowed ten days to pass, after which he gave two more injections, etc., the treatment being continued in this manner for at least four months. Mild and recent cases were thus cured, though in severe cases recurrences frequently took place after a more or less prolonged interval of freedom from the disease. Increasing the dosage to 1 Gm. (15 grains) at every injection resulted in a number of cases of permanent blindness and had to be abandoned. Later, smaller doses were used, such as  $\frac{1}{2}$  grain (0.03 Gm.), gradually increased to 3 grains (0.18 Gm.), administered continuously on alternate days, and kept up for a year or more after the parasites had disappeared from the blood. Combination of mercurial treatment with that by atoxyl was shown by Sir Rupert Boyce, experimentally as well as clinically, to be more effective than that by atoxyl alone.

Really early cases of trypanosomiasis can remain to all intents and purposes cured after a single dose of atoxyl, soamin, arsacetin or tartar emetic. Cases treated by 1 to 3 injections show varying percentages of cures according to dosage and the stage of disease reached. Even cases, the examination of whose cerebrospinal fluid showed them to be in the second stage, have been apparently

cured. Opinion is now in favor of repeated injections of 0.015 to 0.02 Gm. ( $\frac{1}{4}$  to  $\frac{1}{8}$  grain) of atoxyl per kilo. of body weight, *i.e.*, maximum dosage. In a recent epidemic about 250 patients were thus treated in 3 years, and the percentages of cures and relapses to date were about equal. The treatment consisted in weekly dosage of 1 Gm. (15 grains) to adults, to a total of 10 to 12 injections. The value of tartar emetic as an adjuvant to this treatment seems not to be very great, although it may be substituted for an arsenical should toxic amblyopia develop. C. C. Chesterman (Lancet, Nov. 7, 1925).

The manner in which atoxyl acts in trypanosomiasis is not definitely known, though it is generally believed that a direct action on the parasites is exerted. While inorganic forms of arsenic destroy trypanosomes *in vitro*, atoxyl does not act on them very strongly under these conditions. Hence some believe that certain decomposition products of atoxyl in the system are responsible for the trypanocidal action. Ehrlich believed that a product of partial reduction of atoxyl, "trypanotoxyl," which he found strongly trypanocidal *in vitro*, was responsible for the effects, though was not able to show that such a partial reduction took place in the living body.

Whatever be the true explanation of the effects of atoxyl, it is well known that its trypanocidal action soon wears off. Kerandel, who personally took about 70 grams ( $2\frac{1}{2}$  ounces) of atoxyl,—without toxic effects of any kind,—believes that the parasites become atoxyl-fast.

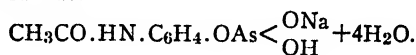
In syphilis the use of atoxyl was recommended by Salmon, Curschmann, and Hallopeau. Uhlenhuth found it to exert a stronger protective

inoculation against syphilis in rabbits than mercury bichloride. On the other hand, the danger of visual and other complications became increasingly manifest with the successive reports of clinicians who used it, and the introduction of other organic arsenicals more effective in syphilis ended its employment in this disease.

Atoxyl has been used with beneficial results in a number of affections in which inorganic arsenic preparations had already been availed of. Among these may be mentioned tuberculosis, leukemia, chlorosis, secondary anemias, exophthalmic goiter, malignant tumors, malaria, and frambesia. Knotte gave subcutaneous injections of 0.2 to 0.4 Gm. (3 to 6 grains) in 18 cases of pulmonary tuberculosis, with results deemed superior to those from cacodylates or tuberculin.

In a large variety of skin affections, including pellagra, psoriasis, dermatitis herpetiformis, chronic eczema, pityriasis rosea, lichen planus, acne vulgaris, pemphigus, chronic urticaria, xanthoma, pellagra, furunculosis, and chloasma, atoxyl has also been used with benefit, although probably having no advantage over the inorganic arsenicals other than its availability for hypodermic use.

**ARSACETIN** is a compound derived from sodium arsanilate (atoxyl) by the replacement of a hydrogen atom in the amino group of the former substance by the acetyl radical. Its chemical make-up is expressed by the term sodium acetyl arsanilate—



It occurs as a white, crystalline body, odorless and tasteless, which is soluble in 10 parts of cold and  $3\frac{1}{2}$  parts of hot water.

It is used by hypodermic injection in doses of  $1\frac{1}{2}$  grains (0.1 Gm.) to  $7\frac{1}{2}$  grains

(0.5 Gm.), and may also be given internally in doses of  $\frac{3}{4}$  grain (0.05 Gm.).

**PHYSIOLOGICAL ACTION.**—Arsacetin acts in the same way as atoxyl, but is said to be from 3 to 5 times less toxic to mammals than the latter.

As regards untoward effects, it appears to be but little superior to atoxyl. Hannes reported 2 cases of blindness out of 142 cases in which injections of arsacetin had been given; he used the drug rather freely, however, injecting, in one of the amaurotic cases, 8 doses of 0.8 Gm. ( $12\frac{1}{2}$  grains) each within sixteen days. Eckard reported 3 cases out of 134, and advised that it be never given in doses larger than  $7\frac{1}{2}$  grains (0.5 Gm.).

Renal irritation appears to be produced with especial facility by arsacetin (Borchers).

**THERAPEUTIC USES.**—Arsacetin has been used for the same purposes as atoxyl and presents the advantage of not being decomposed when sterilized by heat. In **sypilis** the drug has been tried by a number of observers, but its action has been found untrustworthy and evanescent. In **trypanosomiasis** it is considered by Eckard inferior to atoxyl.

Internally, Naegeli and Heinrich have obtained good results with it in **Hodgkin's disease**, and the last-named observer also in **psoriasis** and **lichen ruber**. Doses of  $\frac{1}{2}$  to  $\frac{3}{4}$  grain (0.03 to 0.05 Gm.) 3 or 4 times daily were used and no untoward effects observed.

In **pernicious anemia** Klemperer obtained excellent results by administering subcutaneously 2-grain (0.12 Gm.) doses of arsacetin (in a 10 per cent. solution), gradually increased to 10 grains (0.65 Gm.) in some cases.

**ARSENOPHENYLGLYCIN** is another of the organic arsenicals or arylarsonates introduced by Ehrlich. Its composition is  $\text{NaOOC} \cdot \text{CH}_3 \cdot \text{HN} \cdot \text{C}_6\text{H}_4 \cdot \text{As} = \text{As} \cdot \text{C}_6\text{H}_4 \cdot \text{NH} \cdot \text{CH}_3 \cdot \text{COONa}$ , and it occurs as a yellow powder, readily soluble in water. Different from arsacetin, it decomposes rapidly when left in contact with the air, and must be kept in sealed tubes.

The preparation has been used chiefly in **trypanosomiasis**. Zupitza and von Raven injected as much as 12 to 15 grains (0.8 to 1.0 Gm.) at a dose in early cases, and claimed that it gave better results than

atoxyl. They do not advise its use in advanced cases, however, as the compound proved dangerous when given repeatedly, even in divided doses. The reason for this was found by Fischer and Hoppe, who showed that, while arsacetin is eliminated by the urine in two days and atoxyl in three days, arsenophenylglycin remains in the system for six to eight days, accumulation in the system thus occurring much more readily with the latter substance.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

**ATROPINE.** See **BELLADONNA**.

**AURICULAR FIBRILLATION.**  
See **HEART, DISEASES OF**.

**AUTOINTOXICATION AND ACIDOSIS.**—These two conditions being more or less merged pathologically, they are considered separately to establish clearly their etiological difference.

**AUTOINTOXICATION.**

**DEFINITION.**—Although various disorders may give rise to autointoxication, the form treated herein is that usually meant by the term, *viz.*, intoxication due to poisons absorbed from the gastrointestinal canal.

The writer deems it more rational to attribute the evil effects of intestinal stasis to conditions favoring subinfection and low forms of infection than as a result of chronic intoxication. He considers the term "gastro-intestinal autointoxication" as pernicious. While he deems it possible that the symptoms and diseases enumerated by Lane may follow intestinal stasis, he is convinced at least a large proportion of them may originate independently of such stasis. Before recommending the operation of short-circuiting it is necessary, therefore, to make the fullest studies, so as to discover, if possible, the nature of the organism responsible



for the disturbance and its probable seat of entry. A discovery of the cause of the symptoms is calculated to suggest methods of treatment other than short-circuiting. Only when these have been tried and found wanting is removal or short-circuiting of the colon justifiable. J. G. Adami (Brit. Med. Jour., Jan. 24, 1914).

**PATHOGENESIS.**—Were all food products admitted to the digestive tract submitted to complete digestion and the end-products of the process absorbed by the intestinal mucosa fully prepared, in the physiological sense, for this process, autointoxication of intestinal origin would never occur. But such is not always, and is probably seldom, the case. Some observers have estimated that one-tenth and others one-seventh of the food we ingest fails to be acted upon by the intestinal digestive ferments. Were this undigested fraction at once eliminated per rectum it would cause no trouble; but such not being the case, it is retained sufficiently long in the intestine to putrefy, *i.e.*, to be broken down by bacteria, particularly the putrefactive anaerobes, aided by the colon bacillus. It is the product of this putrefactive process which, absorbed in sufficient quantity and passing into the blood, causes the phenomena of autointoxication.

Carbohydrate decomposition due to the action of bacteria occurs mainly in the stomach and small intestine, while proteid putrefaction occurs mainly in the large intestine.

Emphasis must be laid upon the fact that it is when certain quantities of these toxic products of putrefaction reach the blood that these phenomena occur, since, as stated above, a small proportion of the foodstuffs

ingested undergoes putrefaction under normal conditions. But the body is protected in two ways from the injurious effects of these poisons: (1) by the detoxicatory functions of the liver, which organ the poisons must traverse before they reach the general circulation, and (2) by the anti-toxic constituents or antibodies in the blood proper, of which the poisons provoke an increased production by acting as antigens.

Intestinal toxemia promoting constipation may originate in (1) bacterial by-products of food; (2) autogenous non-bacterial metabolic products from the digestive epithelium, or (3) local bacterial foci in the intestinal wall. Of these, the writer considers the last by far the most important; pathologic examination of over 150 segments of colon tissue removed at operation showed almost complete destruction of many of the important structures of the bowel wall. Satterlee (N. Y. Med. Jour., Dec. 6, 1922).

Experiments carried out to determine the effect of histamine and the absorption of this substance from the alimentary canal.

There is no evidence to prove that the liver is capable of destroying histamine, but the writers assume that there is continual absorption of this substance. In health this absorption is exceedingly slow, chiefly from the large bowel, but when perfect health is not present a considerable quantity of histamine is formed in the small intestine, and from this region is absorbed and produces toxic effects. When the intestinal mucosa was damaged by cutting off the blood supply 5 to 15 minutes the fall in blood-pressure resulting would indicate that histamine was absorbed with a rush. Histamine could be demonstrated in the cecum and transverse colon for weeks after operative relief for intestinal obstruction. Meakins and Harrington (Jour. of Pharm. and Exp. Therap.; Ther. Gaz., Feb., 1923).

Autointoxication is usually attributed to dietetic errors, but, as the above facts suggest, *three* factors should be taken into account: Dietetic errors; efficiency of the liver, and the auto-defensive activity of the blood.

It is not sufficient to show that toxic substances can be formed during the bacterial destruction of nitrogenous matter; it must be demonstrated that these toxins are formed in the intestine, that they can pass through the mucous membrane, that they can escape destruction by the liver and reach the general circulation in amounts sufficient to produce symptoms, and that the symptoms produced by the repeated injection of small doses of these substances into animals are similar to those observed in constipated man. Moreover, the greatest care should be exercised in drawing conclusions from results of experiments *in vitro*, as it seems clear that in the bowel antibacterial forces are at work. It should also be remembered that nearly all the bacteria found in feces are dead, that organisms cannot multiply in constipated feces on account of the dryness and lack of nitrogenous food, and that the great number of intestinal bacteria produce no soluble toxins. Furthermore, absorption cannot take place unless the feces are liquid and churned actively to and fro, whereas the Röntgen ray has shown that the feces begin to harden in the ascending colon and thereafter undergo no churning movements. The fact that the usual symptoms of the constipated disappear so promptly after a bowel movement proves that they cannot be due to absorbed toxins, and they must therefore be produced by distention and irritation of the colon. Such symptoms occur in nervous people, in whom the brain is profoundly influenced by afferent impulses from a distended, overactive and wrongly acting bowel. Many symptoms of constipation are due simply to plugging of the lower end of the canal,

which slows or stops the downward current and produces ripples of reverse peristalsis, which run up the bowel and break into deeper waves in the upper part of the stomach and esophagus. In this way, more than the usual amount of bile is carried back into the stomach and up into the mouth, leading to biliousness, lack of appetite, feeling of fulness after eating a few mouthfuls, coated tongue, etc. The relief experienced after taking calomel is due to restoration of the normal downward currents. Overwork, worry and lack of sleep may also give rise to symptoms attributed to autointoxication, and finally to constipation. In short, nervousness is generally the cause and not the result of constipation. W. C. Alvarez (Jour. Amer. Med. Assoc., Jan. 4, 1919).

**SYMPTOMATOLOGY AND DIAGNOSIS.**—In identifying a case of true autointoxication it is necessary to eliminate other possible disorders. The toxemia may be due to quite another cause, *i.e.*, deficient catabolism of waste products with an accumulation of purin bases in the blood, in other words, the gouty diathesis, often merged with autointoxication of intestinal origin. Imperfect elimination of end-products also complicates chronic nephritis long before the stage of uremia appears. The accumulation of acetone or diacetic acid in the course of diabetes is another form of toxemia for which intestinal autointoxication might be mistaken. This applies also to hepatic torpidity due to cholangitis; gall-stones, even though they may not, as yet, have produced biliary colic; incipient hepatic cancer, and appendicitis attended by gastrointestinal disorders. Intestinal entozoa may also awaken symptoms simulating autointoxication.

The presence of this condition being determined, it is desirable to ascertain which of three underlying causes predominates. While the high liver or individual who eats meat in excess may be ruddy or even appear congested, he will complain of symptoms similar to those described above that would occur in a pale, sallow woman. In the former, the morbid phenomena will be due to excess of proteids over and above his ability to digest them and destroy the poisons in the blood-stream, though, perhaps, both his digestive and antitoxic powers be normal. In the pale woman, on the other hand, both these functions may be deficient and even a small quantity of protein suffice to bring on the symptoms of autointoxication because of the large relative proportion of protein which undergoes putrefaction. The third patient may appear muddy, yellowish and fat, or emaciated—a type often due to hepatic torpor or incipient renal disease of toxemic origin. This shows that the general appearance of the patient is not typical of the disorder, though it affords a clue to the underlying cause.

Headache, often frontal and extending to other parts of the head, finally becomes a true hemicrania; it is sometimes migratory, *i.e.*, moving about from one place to the other. It may be continuous both day and night or recur at fixed intervals, sometimes once or twice a week. The face is apt to be pale during these headaches; there may also be vertigo, considerable lassitude, and, perhaps, nausea. During the intervals, the patient often complains of anorexia, dyspepsia, borborygmus, flatulence, with more or less stubborn constipa-

tion or, rarely, diarrhea. There may be insomnia, or, even if the patient sleeps, fatigue on rising, and drowsiness during the day. Palpitations or arrhythmia and dyspnea on exertion and a stubborn cough are not infrequent, and the sufferer is often irritable. The blood-pressure, excepting in the habitually weak and anemic, is usually high, ranging from 150 to above 200.

When the blood-pressure is very high, however, a renal disorder is apt to be present. Although the urine may prove negative, some severe cases of long standing may show albumin, and also sugar, both of which disappear under appropriate treatment. Debility and emaciation, melancholia and hypochondria, are not uncommon, especially when the paroxysms of headache, the cardinal symptom of the disorder, are frequent and severe. Children are apt to suffer from periodical attacks of fever, which promptly disappear under the influence of a purgative.

Cutaneous disorders, especially eczema and acne, are not infrequently observed. Occasionally there is flushing, icterus, and urticaria. Blood anomalies, chlorosis and anemia, are occasionally noted, especially in females. Various neuroses have been attributed to the same cause; these are treated under their respective heads. A number of eye affections have also been ascribed to autointoxication of gastrointestinal origin.

**TREATMENT.**—In this disorder dietetic measures are of primary importance irrespective of the class—the three referred to above—met with. The main indication is to diminish the proteids ingested, *i.e.*, **reduce meats** especially, to just within the

limits of proper digestibility. In some cases nothing short of **complete meat abstention** suffices; in others it may be allowed from once to seven times a week, *i.e.*, once daily. The **antiputrefactive diet** should then be adjusted to supply daily from 60 to 75 grams (2 to 2½ ounces) of protein and a total amount of 1800 to 2500 calories of fuel value. This diet may be made up mainly of milk, one quart daily; milk soups, bread and butter, cereals, fat bacon, cream cheese, vegetables, fruits, especially bananas; honey, salads, olive oil, and fresh cheese. **Soured milk, curdled milk whey, and buttermilk** are valuable. Metchnikoff's **bacillac, lactobacillin, or bacillus acidophilus** are likewise useful by acting directly on the intestinal flora. Weak tea or coffee may be allowed.

Some patients bear fish without trouble, while any kind of meat, even fowl, will provoke autointoxication phenomena. Fish, poultry, and eggs might be continued once daily each, and only suppressed in turn if these untoward effects continued after the withdrawal of meat, for white of egg also undergoes putrefaction. Constipated individuals should eat copiously of vegetables.

In carbohydrate decomposition cane-sugar is usually the offending agent. Hence, **reduction of sugar and sweets** is often important.

The **dietetic** and other **treatment** suitable in a case of intestinal toxemia of the putrefactive type is illustrated in the case of a woman of 35 years recorded by the writer. This patient had suffered from periodic headaches, dermatographia, indicanuria, spastic colon, a putrefactive stool, and constipation, the latter probably due to regular use of cathartics. No meat or meat

products were allowed for 4 days. Fish, chicken, soups, and gravies were also excluded. Forty grams of protein was allowed a day in cooked white of egg or cheese. Fats, green vegetables, fruits, and an abundance of starch were allowed. At least 1 tablespoonful of **lactose** was ordered taken with each meal. After the 4 days, 3 days of meat diet followed, with omission of lactose, and starches materially reduced. Such alternation of diet was kept up for a few weeks. The patient took no cathartics or enemas, yet rarely passed a day without a movement, had practically no headache, and the indicanuria disappeared. E. J. Best (Med. Clin. of No. Amer., Sept., 1922).

Constipation should be met by salines, preferably **magnesium sulphate**, 1 or 2 teaspoonfuls in a glass of hot water on retiring. Colonic irrigation with **saline solution** two or three times a week is very efficient. In some cases the most satisfactory measure is to inject **olive oil**, 4 ounces (120 c.c.), in the rectum on retiring, to be retained all night. **Castor oil** is the best agent as an occasional purgative in children.

In most cases, especially those attended by debility, pallor, and anemia, **thyroid gland**, 1 grain (0.065 Gm.) during meals, enhances greatly the antitoxic power of the blood. In women this may be advantageously combined with **ovarian extract**, 2 grains (0.13 Gm.).

Where anemia is present **spinach** should form a daily article of diet, owing to its wealth in organic iron, or **Blaud's pill**, 2 grains (0.13 Gm.), and **strychnine**, 1/60 grain (0.0011 Gm.), may be given as chalybeate and tonic. In some cases the curative process is aided by intestinal antiseptics. This is best obtained with **salol**, 5 grains (0.32 Gm.) after meals,

or **creosote carbonate**, 5 grains (0.32 Gm.) in capsules in the middle of each meal to prevent the anorexia and gastric disturbance the latter agent sometimes causes. A liberal intake of **fresh water**, though not during meals, and **out-of-door exercise** are beneficial adjuncts.

In cases of hepatic torpor **calomel** is very useful, especially when 1 grain (0.065 Gm.) is given in six divided doses thirty minutes apart followed by a Seidlitz powder. This given once or twice a week serves to keep the liver, and the flow of bile, which contributes markedly to intestinal antiseptis, sufficiently active in cases unattended by hepatic organic lesions.

The dyspnea met with in these cases is clearly due to meat, since aggravation is caused by increasing the latter, while the symptom disappears when the patient is placed on a milk diet. It is evidently due, as suggested by Huchard, to vasoconstriction (of the arterioles), for the pallor which accompanies the dyspnea likewise ceases. If slight edema is present **theobromine** is indicated to enhance the functional activity of the heart and kidneys.

### ACIDOSIS, OR ACID INTOXICATION.

The body protects itself against the morbid influence of various acids in three ways: (1) Acids displace carbonic acid from the sodium bicarbonate and set carbon dioxide free. The latter is then removed by increased pulmonary ventilation—hyperpnea, *i.e.*, increase of respiratory movements or exchanges, leaving a neutral sodium salt (oxybutyrate, chloride, etc.), which the kidneys can readily eliminate. (2) Elimination of the acid, as shown by the ability to excrete an acid urine when the blood is nearly neutral. (3) The production in the body of an alkali, ammonia, capable of neutralizing the acid.

Van Slyke emphasized the fact that acidosis may also be caused, not only by an overproduction of acids, but also through retarded elimination of them.

The original meaning of the word "acidosis" when introduced by Naunyn was that of an intoxication due mainly to beta-oxybutyric acid, which Kunz and Minkowski had recently discovered in the blood and urine of diabetic cases, and in a minor degree to the chemically allied substances, aceto-acetic (diacetic) acid and acetone.

As stated by M.-P. Weil (*Monde méd.*, May 15, 1924), however, this was far too narrow a conception of acidosis, which may occur in the absence of acetone bodies and be attended with the presence in the tissue fluids of an excess of phosphoric, carbonic or lactic acids or even, perhaps, of sulphuric, hydrochloric, acetic and other acids. Conversely, there are diabetics whose urine is rich in ketone bodies without their being in a condition of acidosis. It is thus necessary to avoid confusing ketosis, due to the ketone bodies, with acidosis, implying a condition attended with lowered alkalinity of the blood or acidemia.

**Etiology.**—We have seen under Acetonuria that acetone acidosis may be due in children to the excessive consumption of fats, cream, etc. Acidosis with decreased alkalinity of the blood is usually due in normal children to a diet in which basic salts, such as those supplied by vegetables, cereals, citrus fruit, etc., are too scant. Such children show as prominent symptoms recurrent vomiting and hyperpnea, or exaggerated respiration without cyanosis. Acidosis is also commonly observed in infantile diarrhea.

Pregnancy may also give rise to acidosis, probably owing to the excessive use of the maternal basic salts by the fetus. W. S. Gordon warns that one should be especially on the watch for a toxemia from this source which is not accounted for by kidney involvement or the retention of urea; otherwise grave and unsuspected complications may develop.

According to observations of A. Hunter, there seems to be among nephritic cases no relation between the degree of the acidosis and the severity of the dyspnea. It would seem that in cardiac cases without renal involvement the dyspnea is due

to several different causes, including acidosis, obstruction to the gaseous exchange in the lungs, and hyperexcitability of the respiratory center.

In a study of 68 normal pregnancies, however, L. A. Emge (Amer. Jour. of Obstet., Nov., 1916) found, with the aid of 4 tests, that acidosis was present in the great majority of instances. In view of his results he suggests hesitation in drawing conclusions as to its significance.

Many other disorders, medical and surgical, may also cause acidosis. Thus Crile (Trans. of the Med. Soc. of the State of New York, Apr. 26 to 29, 1915), in enumerating the conditions in which it occurs, mentions the fatigue of the athlete, Graves's disease, fever, emotions, cyclic vomiting, Bright's disease, surgical shock, anesthesia by ether, chloroform, nitrous oxide, toxemias due to intestinal stasis, asphyxia, starvation, diabetes, and other conditions. These are regarded as activators of energy transformation through the adrenals which they stimulate, causing an abnormal output of adrenin, thereby increasing respiratory activity and oxidation, and leading to an increased production of acid by-products.

[This generalization is too broad. We doubtless have increased oxidation and metabolism as a result of an increased output of adrenin (rôles which, by the way, my own labors first pointed out), with the co-operation, I would add, of the thyroid secretion. We cannot, however, attribute *all* the forms of acidosis mentioned to this process. Thus, cyclic vomiting, shock, starvation, deficiency of carbohydrates, and other conditions are not promoters of "excessive kinetic activations," as Crile words it, but rather of the reverse, *i.e.*, of disorders in which oxidation and metabolism are slowed. When such is the case, the normal balance between the acids and bases (mainly sodium bicarbonate) in the plasma is disturbed, and acids accumulate in the blood (*acidemia*) *passively*, *i.e.*, owing to deficient catabolism and elimination of their end-products. Indeed, from my viewpoint, we should recognize, with the ductless glands as participants in the etiological process, at least three general types of acidosis:—

1. *Passive acidosis due to deficiency of basic salts*, mainly sodium bicarbonate, as in recurrent vomiting, due to foods lacking in basic salts, infantile diarrhea with acetone breath (acetone here because the food administered is rich in fats, such as those in cream, rich milk, butter, etc.), starvation, gastric ulcer, diabetes with acetone breath (due to deficiency of lipase), surgical shock, cardiovascular lesions in the aged, for example.

2. *Active acidosis due to overproduction of acids* as wastes in the course of excessive metabolism, as in violent exercise, athletics, intense mental excitement or labor, pregnancy, etc.; or produced as a result of abnormal autodefensive activity, as in acute fevers. Graves's disease of toxic origin, toxics of intestinal origin, chloroform, ether, cancer, hepatic and gastrointestinal disorders of an adynamic type, autoinfections of tonsillar, gingival and nasal origin, etc., in all of which the ductless glands are overactive.

3. *Obstructive acidosis due to renal, intestinal and cutaneous disorders* in which the elimination of acids is inadequately performed or arrested, as in Bright's disease and other organic disorders of the kidney, nephrectomy, constipation, extensive burns, etc., causing not only retention of acids with other wastes, but increasing the activity of the ductless glands as factors of the defensive mechanism, thus still further augmenting wastes including various acids.

The importance of discriminating between these three classes asserts itself especially when the therapeutics of acidosis is in question. C. E. DE M. S.]

**Symptomatology.**—The salient symptoms of acidosis due to *miscellaneous causes* are hyperpnea, or increase of respiratory movements, the purpose of which is to hasten the elimination of the acid, sighing respiration, nausea, and, in severe cases, vomiting, which may be brought on by the mere act of swallowing and a sweetish apple-like odor of the breath. All these symptoms are, of course, in addition to those of the causative disorder.

In *diabetes* a severe degree of acidosis, which may occur irrespective of any suggestive indication in the urine, may give

rise to headache, vertigo, faintness, somnolence, nausea and vomiting, and hyperpnea, or air-hunger, besides the peculiar apple-like odor of the breath. These symptoms should be taken jointly as danger signals of impending diabetic coma.

In children *intermittent vomiting* is commonly observed, the attacks recurring usually every three or four weeks in most instances. It is mainly observed in high-strung, nervous and hypersensitive subjects. Besides the sweetish breath, there may be dryness of the tongue, mouth and pharynx, and thirst. Fever, ranging from 102° to 104° F. (38.9° to 40° C.), may develop. In mild cases such an attack may occur after dietetic indiscretion, particularly in children that have been subjected to a diet mainly composed of milk, and other foods in which basic salts are scant.

In the more severe cases, a stuporous or even semicomatose condition and marked fever may appear. The eyes seem sunken and have dark circles about them. A typhoid state with profound toxicity, or meningitis, may be suggested. Vomiting is pronounced and marked by the slightest quantities of food or fluid ingested. Abdominal and gastric tenderness may be such as to suggest appendicitis. Edema and icterus may also appear (Fischer). Howland and Marriott have referred to a diminution of the output of urine as striking evidence of acidosis in infancy.

In a study of the relationship between acidosis and *diarrhea* in 200 infants, Schloss and Stetson found that those suffering from severe diarrhea with toxic symptoms often show the following signs of acidosis: 1, decrease of the carbon dioxide of the blood and alveolar air; 2, decreased carbon dioxide combining power of the blood plasma; 3, high ammonia coefficient in the urine; 4, increased tolerance to sodium bicarbonate; 5, improvement of the symptoms after administration of sodium bicarbonate. These signs are evident in some cases of diarrhea before the typical symptoms of intoxication have developed, and serve as a warning and therapeutic indication. If an infant suffering from severe diarrhea has hyperpnea, the diagnosis of acidosis is almost certain. If hyperpnea is not observed the diagnosis of acidosis must rest on laboratory evidence.

A form following *weaning* has been described by Abt. At first there are vomiting and diarrhea, and, later, rapid breathing, pallor, and obstinate constipation. The urine contains tyrosin and leucin, as well as acetone and diacetic acid.

Morse has laid stress on cases following *bacterial infection*, general or originating from a local focus, in children, and Williams, on instances due to *toxic foods*, including mussels and ice-cream.

Acidosis has been mainly considered due to an increase of the acids, particularly the organic acids. But reduction of the bases may likewise bring about acidosis, and the authors recognize 3 forms, *viz.*, those arising through hyperacidity, through hypoalkalosis, and through both combined. The group of the acidoses through hyperacidity may be further divided into acidosis from excess of ketone bodies, or ketoacidosis, such as occurs in hydrocarbon starvation and diabetes; acidosis from excess of lactic acid, or lactoacidosis, which has been observed after violent and prolonged muscular exertion and probably plays a rôle in some diseases; acidosis from excess of hydrochloric acid, or chloroacidosis, met with in nephritis when elimination of chlorine is defective, and also produced by administration of large amounts of calcium chloride or ammonium chloride; acidosis due to proteins which seize upon bases, or proteinoacidosis, a condition which infiltration permits of demonstrating and which occurs in some cases of heart disease with edema. Acidosis through hypoalkalosis is by no means rare, and is a frequent cause of the acidosis in Bright's disease. The authors found it in 2 cases of osteomalacia; it may, perhaps, be concerned in the acidosis of rickets. Acidosis through combined hyperacidity and hypoalkalosis is met with in Bright's disease and more rarely in the extreme stages of diabetes. L. Blum and M. Delaville (*Presse méd.*, May 9, 1925).

**Diagnosis.**—The information afforded by acetone tests is unreliable in the sense that acidosis may be present and acetone

fail to appear in the urine. A negative acetone test affords, therefore, no diagnostic information. The clinical signs of acidosis, however, plus simple office tests, are virtually conclusive.

[Thus, even if acetone tests fail, we have (1) hyperpnea, or air-hunger, and inability to hold the breath (*vide infra*) more than 30 seconds; (2) and the **methy-red test** (the *solution*—available at chemists'), 1 drop of which, on filter-paper wet with the urine (avoiding ante-breakfast urine), turns it red, thus indicating acidity (which would be yellow if the urine were alkaline), acidosis is undoubtedly present. If besides these signs there is recurrent vomiting the acidosis is severe. The degree of severity may be gauged by dropping on the same wet paper *para-nitro-phenol*. If the urine is alkaline or weakly acid, the spots will turn yellow with a tinge of green; if strongly acid, no change of color will be noticed, thus indicating a strongly acid urine and intense general acidosis. Or, a drop of *dilute phenolphthalein solution* in a sample of urine will turn it pink or crimson if alkaline, according to the intensity of the alkalinity, but if acid no change of color will be observed. Litmus-paper is useless, and often misleading. C. E. DE M. S.]

Again, the presence of *betaoxybutyric acid* in the urine may prove of diagnostic value, for it never occurs normally. It is often associated with acetonuria and diaceturia in diabetes, sometimes in fever, and has been thought by von Jaksch to be the immediate cause of diabetic coma. Its presence may be ascertained in various ways. Among these may be mentioned the **polariscope test**. If a urine be levorotatory after fermentation with yeast, it is strongly probable that this acid is present. This may be confirmed by means of **Kulz's test**. After fermenting the urine with yeast it is evaporated to a syrupy consistence. An equal volume of concentrated sulphuric acid is then added and the mixture distilled without cooling; alpha-crotonic acid is produced, which is distilled and, after strongly cooling, the distillate is collected in a glass. Crystals which melt at 72° C. separate. If no crystals be obtained, the distillate should be shaken with ether and the melting point

tested with the residue, which has been washed with the water obtained after evaporating the ether. (See also ACETONURIA, Volume I).

An important means of detecting acidosis is **Marriott's alveolar air test** (alveolar carbon-dioxide tension determination). In this procedure about 600 c.c. of air are blown into a 1500-c.c. rubber bag. At the end of a normal expiration, the patient takes the attached tube in his mouth, holds his nose closed between the fingers, and breathes into the sac 4 times in twenty seconds, finishing with an expiration. Analysis of the expired air in the sac is to be begun within three minutes. Two or 3 c.c. of a standard sodium bicarbonate solution containing a little phenolsulphonphthalein are placed in a test-tube of the same diameter as the tubes containing standard color solutions, and air from the rubber bag blown into the solution through a tube with narrow outlet until the color change in the bicarbonate solution ceases. The color obtained is then promptly compared with those in a series of 8 standard tubes, labelled 10, 15, 20, etc., up to 45, these figures relating to the carbon dioxide tension in millimeters. The color relationship of the specimen to the standards can be rather exactly found and a reading made within 1 mm. by placing the specimen between the 2 standard tubes which it most nearly matches and comparing it carefully with them. The normal tension in adults at rest is from 40 to 45 mm. Mild acidosis is indicated by 30 to 35 and imminent danger by 20 mm. In coma with acidosis, 8 to 10 mm. may be read. The tension is 3 to 5 mm. lower in infants than in adults. In obtaining the air specimens from infants, a rubber dam face mask and 500 c.c. rubber bag may be used.

An acidosis is said to be "compensated" when the actual reaction of the blood has not materially changed in spite of depletion of the alkali reserve owing to the addition of an excess of acids. Diminution of reserve alkali corresponds with decrease of alveolar carbon dioxide. "Uncompensated" acidosis begins when, the alkali being gradually used up to neutralize acids, the supply of bicarbonate begins to fail, and an actual change in the reaction of the blood sets in. At this point symptoms appear, and the



carbon dioxide tension sinks very low. In diagnosis, *determination of the alkali reserve* is the most direct and reliable procedure (see under HEMATOLOGY, Vol. V). The indirect methods—alveolar carbon dioxide tension and alkali tolerance,—however, also yield useful inferential information.

The **Sellards alkali tolerance test** is based upon the quantity of sodium bicarbonate which can be administered to the patient without rendering the urine alkaline. It is carried out by giving 5 Gm. (75 grains) of sodium bicarbonate by mouth in a moderate amount of water at intervals of 2 or 3 hours. The urine should be voided before each administration and unless the urine is distinctly acid it should be boiled thoroughly in order to convert the bicarbonate into carbonate so that it will react readily to litmus.

In chronic nephritis, the deficit of sodium bicarbonate may amount to as much as 40 or 50 Gm. daily (*i.e.*, 40 or 50 Gm. of sodium bicarbonate may be required to render the urine alkaline), before any positive clinical signs of acidosis will develop in a patient who is not taking active exercise. With a deficit of 75 to 100 Gm., distinct dyspnea is observed after moderate exercise, and where it rises to 110 Gm. mental confusion begins. Where the system will tolerate 150 to 200 Gm. of sodium bicarbonate uremia occurs, with definite air hunger and coma. A deficit of more than 200 Gm. is usually followed by death (Sellards).

Y. Henderson found that *inability to hold the breath* at all is a sign of acidosis in its acute stage. The normal period is between 30 and 40 seconds; any period under 20 seconds indicates acidosis.

**Iodine Urine Test.**—To 145 c.c. of water (hydrant water will do) are added 3 c.c. of Lugol's solution and 2 c.c. of a saturated solution of picric acid, the whole being thoroughly mixed. The result is a fine clear reddish liquid of bright color. Pour this liquid into a white dish and heat it on the water bath to a temperature of 180° F., but if a water bath is not available it may be heated over the flame until fumes are abundantly given off, boiling being avoided by turning down the flame sufficiently.

When thus heated, the urine is added as quickly as possible but in small amounts at a time, using for this purpose a graduated buret. In acidosis the amount of urine needed to turn the bright red color to a bright yellow color is small, and the smaller the worse the case. In severe cases 2 or 3 c.c. of urine will almost immediately discharge the red color. In cases of moderate severity 8 or 10 c.c. may be required. Mitchell (Med. Record, Mar. 8, 1919).

**Prophylaxis.**—In *surgical acidosis* prophylactic measures have been increasingly employed. The warning signs of pre-operative acidosis are: (1) A history of unaccountable headaches, vertigo, attacks of dyspnea, occasional nausea or vomiting, an unreasonable dread of the operation, tachycardia, and other nervous symptoms. (2) Sweetish odor of the breath. (3) Presence in the urine of acetone bodies.

As to preoperative prophylaxis, in 138 major operations Quillian had no mortality and but 5 cases of shock by resorting to the following prophylactic routine: **Sodium bicarbonate**, 5ss (2 Gm.) in one-half glass of water *t. i. d.*, one-half hour before meals, for two days preceding operation. The same salt and **glucose**,  $\bar{a}\bar{a}$  5ss (15 Gm.), with water, q.s. ad  $\bar{v}$ vij (240 c.c.), as a retention enema, *b. i. d.*, for two days preceding operation. **Liquid diet** and large quantities of water for 48 hours preceding operation, but no butter-milk or egg-albumins for 24 hours.

The morning preceding the day of operation, **castor oil**, 5ss (15 c.c.). **Soapsuds enemata** the night preceding, and the morning of, the operation. **Strontium bromide**, gr. xxx (2 Gm.), the night preceding operation to insure a good night's rest. **Morphine**, gr.  $\frac{1}{8}$  (0.008 Gm.), with **scopolamine**, gr.  $\frac{1}{400}$  (0.0006 Gm.), one hour preceding gas and ether anesthetic.

After operation **sodium bicarbonate**, 5ss (2 Gm.), in one-half glass of water one-half hour after meals for several days. **Water and liquid diet** as soon as nausea ceases, and continued until a light diet is begun on the fourth day.

**Treatment.**—In the treatment of *acidosis in infants and children*, according to Hess

(Northwest Med., Nov., 1923), large amounts of **water** should be given by mouth; if it is not retained, subcutaneous or intraperitoneal use of **normal saline** or **Ringer's solution** is advised, the latter as often as every 6 hours, if necessary, during the early treatment. In non-diabetic acetone body acidosis, **dextrose** should always be given, either by mouth, rectum or intravenously. By the mouth, a 5 to 10 per cent. solution may be given every 2 to 4 hours, in quantities varying according to age and gastrointestinal tolerance. By rectum, a 5 per cent. solution may be given to the amount of 60 to 120 c.c. (2 to 4 ounces) every 3 or 4 hours; in young infants and older children who are not too restless the drip method may be used. Intravenously, 5 or 10 per cent. dextrose in Ringer's or saline solution may be given in amounts of 60 to 300 c.c. (2 to 10 ounces), repeated as indicated. Dextrose rather than bicarbonate is the prime agent for non-diabetic ketosis or lactic acid acidosis. When the alveolar carbon dioxide tension is above 30, recovery is usually spontaneous and bicarbonate unnecessary. If it is given, **sodium bicarbonate** should be used by the mouth, 1 to 2 Gm. (15 to 30 grains) in water at 4-hour intervals, or intravenously, in a 2 per cent. solution in the quantities already mentioned for dextrose.

When the urine becomes amphoteric or alkaline to litmus, further administration should be withheld, unless the urine again becomes more acid than normal.

As soon as the stomach can retain inert fluids—usually not over 6 to 12 hours—**carbohydrates** should be given by the mouth. Thick **cereal pastes**, to which **cane sugar** or **maltose-dextrose compounds** have been added, are usually best retained, and may be given in small quantities at 2-hour intervals.

Hyperpnea and bright red lips are significant of acidosis, according to W. P. Cornell (Arch. of Ped., Feb., 1924), who divides the cases, with their treatment, into 5 distinct types: (1) *Urinary acidosis*: **Water** to be given freely and patient watched for sighing and air-hunger. (2) *Acidosis with vomiting, but without fever or leukocytosis*: **Sylvester orange-juice treatment**: Strained, ice-cold orange-juice in teaspoonful doses every 5 minutes until vomiting stops; then,

after ½ hour, 2 teaspoonfuls every 5 minutes until vomiting has stopped for ½ hour; then 4 teaspoonfuls, and so on until 1 ounce of juice is retained each 5 minutes for ½ hour. The **juice of canned pineapple** may be substituted for orange juice in the same dosage, and either juice may be further sweetened with **honey**, **dextrose**, or even **cane sugar** or **corn syrup**. In desperate cases, **sodium bicarbonate** intravenously, by enema or intraperitoneally in 5 per cent. solution, or **dextrose** intravenously or by enema in 5 to 7 per cent. solution. (3) *Acidosis with vomiting, fever and leukocytosis*: Same treatment, together with discovery and prompt **treatment of the focus of infection**. (4) *Diarrheal acidosis*: Both **salts** and **water** to be supplied. Enough **carbohydrate** must be available for normal fat combustion. In severe vomiting, precluding sufficient ingestion of carbohydrate, **insulin**, properly used, should rapidly check the acetonuria and nausea, thus permitting of food retention; its use is unsafe, however, without blood sugar estimations. (5) *Acidosis with profound toxemia*: Rather hopeless; anything and everything should be tried.

In *operative acidosis*, A. C. Burnham recommends: (1) Adequate nutrition by mouth, especially in the form of **carbohydrates**; (2) forced carbohydrate feeding in the form of **dextrose solutions** by mouth—a teaspoonful of dextrose to a glass of water. It may also be given by rectum, or subcutaneously, an ounce to a quart; (3) **bicarbonate of sodium solutions** given by mouth, rectum or subcutaneously; (4) saline solutions by **hypodermoclysis** during the operation; and (5), **morphine** for the relief of pain and to prevent the evil effects of excessive external stimuli.

Post-operative acidosis was first successfully treated with **insulin** in non-diabetic cases by Thalhimer. At least 2 Gm. of **dextrose** should be given for every unit of insulin injected.

In *acidosis after etherization*, G. G. Smith (Boston Med. and Surg. Jour., Apr. 21, 1921) found that the fact that, when nauseated, the patient cannot take water, increases the symptoms. One subpectoral injection of a liter (quart) of normal **salt solution** will usually break the vicious circle. It is far better, however, to anticipate the

lack of fluids by: (1) Forcing fluids until 1 or 2 hours before operation; (2) immediately after operation giving either a sub-pectoral infusion or 3 pints of tap **water by rectum**. After that, the **Murphy drip** may be used or tap water may be given rectally, 8 ounces (240 c.c.) every 6 hours.

Case of *acidosis following trauma* in a non-diabetic 11-year old boy. **Insulin**, 25 units of H-20, was given intravenously together with 200 c.c. (6¾ ounces) of 10 per cent. **glucose** solution. This was followed by a **hot coffee enema** and a **rectal drip** of 5 per cent. **sodium bicarbonate**. The patient took very slowly about 4 ounces (120 c.c.) of **orange juice** by mouth. Improvement followed and, under further like treatment, recovery. G. Ginsberg (Jour. Amer. Med. Assoc., May 10, 1924).

Four cases of acidosis after plastic operations, including 3 on bones, in children. One patient died. The condition is ascribed to fat embolism. The treatment consists of **saline infusions**, **dextrose injections**, and **sodium bicarbonate**. Fickenwirth (Zent. f. Chir., Dec. 12, 1925).

Acidosis in various disorders such as diabetes, shock, diarrhea, etc., is considered under the respective headings.

C. E. DE M. SAJOUS,  
Philadelphia.

## AUTONOMIC IMBALANCE.

**DEFINITION.**—Autonomic imbalance (*ataxia autonómica*; *autonomic ataxia*; *ataxia vasomotoria*; *vasomotor ataxia*) is a condition—manifested in greater or less degree by certain individuals, forming probably about one-twentieth of the human race—of facile disturbance and aberrant performance of the autonomic functions, *i.e.*, the functions of the sympathetic and parasympathetic—or, as it is also called, in whole or in part, the vegetative, or involuntary, or splanchnic, or visceral—nerve system, and especially of its vasomotor division.

[We reject the proposed division of the involuntary nerve system into autonomic and sympathetic. The sympathetic is a *part of*, not *apart from*, the autonomic as described by Langley.—S. SOLIS-COHEN].

## CLINICAL MANIFESTATIONS.

—The condition may be conceived as a state of unstable or precarious equilibrium, or as a tendency to unbalanced—incoördinate—action. It is not in itself disorder or disease; but it is a foundation upon which many and diverse forms of disorder or disease may be erected. It is an aberrant constitution. In some persons the degree of constitutional abnormality is so slight that it is merely a potential source of disorder—a liability that may never come to actuality; in others it results in almost continuous discomfort; in still others it gives rise from time to time to seizures or spells attended with greater or less distress, and even with danger. Its recognition is thus not of mere academic interest, but of consequence to the welfare of the patient.

It may be manifested by excess or defect, of excitability or of inhibition,—thus, by undue readiness (*crethism*) or by sluggishness (*apathism*) of reaction. But the general result is the same; there is a maladjustment of functions, which may be shown throughout the entire range of autonomic nerve distribution, or in a limited part thereof; and, by reflex, may in some instances disturb the action of cerebrospinal nerves.

The cardiovascular system exhibits the most frequent and most easily recognized disturbances of balance; not so much in alterations of the heart's rate and rhythm—though these do occur—as in ischemias, in active or passive hyperemias, in

edemas, in excessive and diminished secretions. Such derangements of peripheral circulation are most readily observed on the skin and the visible mucosæ, but no organ and no region is exempt. So, too, all the functions are liable to disorder; not only as a result of vascular aberrations but also through change, primary or secondary, in the nerve impulses, hormones and other influences acting upon secretory, motor, sensory cells. Not alone circulation, then, but respiration and digestion, secretion and excretion, the action of unstriated muscle fiber throughout the body and even at times, of the skeletal muscles, pain and thermal sensations, vision, hearing, touch, taste and smell, even cerebration, may under certain causative conditions be deranged. In brief, the symptoms exhibited, whether local, diffuse or general, are multiple and diverse. They may be multifunctional and multi-regional as well as multiform. They are often paroxysmal, sometimes painful, and are always suggestive of instability, *i.e.*, of failure in the regulatory mechanism—want of taxis, ataxia.

Individuals, the subjects of autonomic imbalance, may thus fail to react promptly or adequately to stimuli, internal or external, that ordinarily excite balance-preserving reactions; or they may react (*a*) to stimuli that do not excite observable reaction in the great bulk of mankind, and (*b*) to stimuli of like kind but less moment, than those exciting similar reactions in their normal fellows. Their reactions to disturbing stimuli of kind and moment appropriate and adequate to excite derangement in the normal person are unbalanced or ex-

cessive, and often bizarre. Restoration after derangement is unduly protracted, and disturbances, once excited, tend to recur. Recurrences may gradually assume the form of consistent, organized syndromes; or they may vary from time to time in curious fashion. Not rarely a new symptom, or group of symptoms, will be engrafted upon the original syndrome; or a symptom or symptom-group may disappear, and its place be taken by others; or varied symptom-groups may appear, disappear and reappear in a somewhat capricious manner. As a rule, the symptoms are exaggerations, sometimes caricatures, of the physiologic and pathologic reactions of the ordinary person.

To give a brief general view by examples: In one subject a slight touch—hardly to be called a blow—upon the skin, will produce circumscribed (angioneurotic) edema, or even extravasation of blood. In another a slight indiscretion in diet will be followed by swelling of one side of the face and lips. In another, without discoverable cause, “blood blisters” (acute varices) will appear in the pharynx, or blood-spitting, which originally had given rise to suspicion of tuberculosis or of gastric ulcer, will indicate their appearance in bronchus, esophagus or stomach. In another, strong emotion, pleasurable or the reverse, tends to excite edema of the tongue or larynx; in another, either fatigue or the use of certain foods will be followed by the appearance of numerous small bullæ on the feet. One suffers today with urticaria and next week with asthma; another has paroxysms of migraine alternating with gastric crises, and sometimes attended with mucous

enteritis, while a third suddenly loses the tendency to migraine and presents instead Graves's phenomena, Raynaud's phenomena, or a mixture of both. One will manifest paroxysms of acroasphyxia with mild vertiginous symptoms; another, with constantly dusky hands, has no marked disturbance of functions or perhaps suffers with hay fever in its due season; while a third will have hay fever in spring and periarticular swellings in the fall, with perhaps paroxysms of tachycardia or bradycardia, and a fourth shows now erythema nodosum, and again spastic symptoms referable to the biliary, the intestinal or the urinary tract. Indeed, the possible permutations of association, alternation and variation are literally incalculable.

In no person are all the phenomena invariable; in few is there but a single group of manifestations; in none are the exciting causes always definite and the same; but in all, certain stigmata of the condition are constantly or intermittently present, and upon their recognition, together with the personal and family history of the patient, depends the diagnosis. They are discussed, therefore, under the latter head.

The supposition that these derangements always imply an excessive tonus throughout the entire range of one or the other of the opposing groups of autonomic nerves derived from the craniosacral or thoracolumbar ganglia, respectively (*i.e.*, so-called "vagotonia" or "sympathicotonia") is erroneous; and the introduction of these terms by Eppinger and Hess (1910) in place of that long before (1890) published by the writer has even less warrant than the prop-

osition by Morichau-Beauchant (1910) of the term "angioneurotic diathesis," or than the tendency of some writers to interpret certain of the phenomena as evidences of hyperthyroidism.

[The designation "angioneurotic diathesis" is too limited to cover the entire field described by Morichau-Beauchant, whose communication, indeed, is almost a *verbatim* translation of the paper on "Vasomotor Ataxia" published by the writer 17 years earlier.—S. SOLIS-COHEN].

"Mixed" cases are, if not the invariable, at least the common observation. In 40 years the writer has not seen among thousands of cases a single instance that could be called pure "vagotonia" or pure "sympathicotonia." Nor is it at all certain that many of the phenomena attributed to excess in one direction are not, in fact, the result of defect in the other. We can be sure of one thing only, *viz.*, that *balance* is deranged—that there is an *ataxia*.

**HISTORY.**—Many and varied conditions of disturbance of the physiologic balance of the autonomic nerve system in general, and of the vasomotor nerve system in particular, have been recognized—and in some instances long and commonly—under distinctive nosologic terms. Examples of these are: Graves's syndrome, migraine, asthma, hay fever, urticaria, angioneurotic edema, angioneural arthroses (hydrops articularum vasomotoria intermittens), visceral angioneuroses, angina vasomotoria, erythromelalgia, Raynaud's syndrome. But there are many others not so sharply defined; and often the phenomena—as in cases, *e.g.*, of biliary, ureteral, intestinal, or appendicular colic—closely resemble those of organic origin, and may be difficult to discriminate therefrom.

The term *vasomotor ataxia* was first publicly used by the writer in 1886. In medical journals for many years there had appeared reports with vague titles such as "A Curious Case," "A Case for Diagnosis," "Unique Vasomotor Disturbances," etc. Trousseau and others had written upon "functional

neuroses," and Allbutt (1884) had treated extensively of the "visceral neuroses," recognizing their association with "migraine, cardiovascular instabilities and the like," but hesitating to accept vasomotor disturbance as the explanation.

The close connection between asthma and urticaria, with their alternating appearance in the same individual, had been commented upon by many observers, and was recalled to attention by Bulkley (1885). The terms "spasmophilic diathesis" and "exudative diathesis" came to be applied, especially by German writers, in explanation of a group of phenomena including some of those under consideration in this article. "Herpetism" and "arthritism" had long been used still more vaguely in France.

Osler in 1888 wrote on "hereditary angio-neurotic edema," and between that date and 1904 called attention, in a number of papers, to the "visceral complications and crises of the erythema group of skin diseases," and particularly to their surgical relations. In 1897 Dana described the phenomena of "vascular throbbing in certain neurasthenic conditions" as "angiopathic neurasthenia." Cassirer (1901) published an elaborate monograph upon "vasomotorial-trophic neuroses." Savill discussed (1901) the angio-neurotic disorders of the extremities as instances of "vasomotor incoördination." In 1902 Hans Herz, in avowed elaboration of the writer's paper of 1893, issued a monograph on "the neuroses of the peripheral circulation" with the alternative title of "vasomotor ataxia."

It was in 1884 the writer encountered the first, and in 1886 that he presented in Bartholow's clinic at Jefferson Medical College Hospital the second, of the series of cases for which he coined the title of *vasomotor ataxia*; and under this designation he showed in successive years to his classes at Jefferson Hospital and at the Philadelphia Polyclinic a number of other instances, some of which were published as case reports or in reports of his lectures. In 1893 he read before the first Pan-American Medical Congress a paper entitled "Vasomotor Ataxia; A Contribution to the Subject of Idiosyncrasies" which was based upon 64 cases observed up to that time (Amer. Jour. Med. Sci., Feb., 1894). These 64 cases were

shown to be of 3 classes: (a) Characterized chiefly by relaxation of vessels [Graves type; angio-ectatic (Herz)]; (b) characterized chiefly by constriction of vessels [Raynaud type; angio-spastic (Herz)]; (c) characterized by coincident relaxation and constriction in different regions or alternating relaxation and constriction in the same region (mixed). The mixed cases were shown to predominate greatly, while purely relaxant or purely constrictive cases were held to be existent but rare. It was also pointed out that neither relaxation nor constriction could always be interpreted with certainty either as excessive or defective activity of either constrictor or dilator nerves, but merely as a *rupture of the balance* in one or other direction. Hence, as a general descriptive term, neither angio-spasm nor angioparesis would be correct, although in given instances, one or the other might be applied to certain of the phenomena. Moreover, as pointed out by Hans Herz, the tissue spaces as well as the vessels are involved in some of the phenomena.

Later, as the writer's clinical and other services enlarged, and, especially, as a greatly increased number of Russian Jewish refugees—victims of persecution, and subjects not only of personal emotional disturbance, but also of what might be termed hereditary anxiety—came under his observation, the number of instances mounted into the thousands, and he ceased to keep the tally. Moreover, his concept of the condition broadened. It became obvious, as was, indeed, stated in the paper of 1893 and in another in 1898, that not only the vasomotor balance, but that of the whole involuntary nerve system is involved. The term *autonomic imbalance* was used in discussing in 1898 and again in a paper of 1909, reporting 200 cases of various visceral disturbances, and under the title (altered from Allbutt's) of "visceral angioneuroses," and in a paper published in 1912 (Med. Review of Reviews) the title *ataxia autonómica* was formally proposed, to cover the whole field of which vasomotor ataxia is a part, and perhaps the most important part.

Of the 200 cases reported in the writer's 1909 paper no 2 were exactly alike. They involved, among them, every region of the body and every physiologic function. None

was confined to a single organ, tissue, or function, but some were relatively simple and others quite complex. Examples of the simpler forms of disturbance were:

CASE I. Angioneurotic edema of tongue, pharynx, and larynx; gastroenteric crisis; anginoid crisis. (Case of 40 years' duration, with edema of various parts of the body.)

CASE IV. Paroxysmal epigastric pain or abdominal cramps; marked eye signs; no goiter; occasional palpitation; transient pigmentations; acrocyanosis; local syncope.

CASE V. Paroxysmal nausea; local cyanosis (of hands and nose); eye sign; nail signs; tuberculous and gouty family history.

CASE VII. Hyperacid gastric crises; epistaxis; hay fever in substitution for æstivo-autumnal diarrhea; nail signs; dermatography; hives; nocturnal muscular spasm; angioneurotic family history.

CASE XII. Patient operated upon for hepatic colic, nothing found; cardiac palpitation; epistaxis; hemoptysis; bleeding hemorrhoids; eye signs; nail signs.

CASE XIII. Hepatic colic; operation, no lesion; eye signs; nail signs; dermatography, etc.

CASE XX. Arterial throbbing, simulating thoracic aneurism in a case exhibiting gastroenteric crises; dermatography; factitious urticaria; epistaxis; eye signs and nail signs.

CASE XXVI. Old retinal hemorrhages in a patient showing the signs of vasomotor ataxia and without discoverable visceral or hemic lesion.

CASE XXIX. Pigmented spots following a localized punctate eruption in a patient formerly exhibiting gastric crises; eye signs; tricolored nails; thyroid enlargement; palpitation.

CASE XXXVI. Erythema exudativum following acute gout (?) in a subject of chronic Graves's disease, subject to gastrointestinal crises.

CASE XLV. Pseudoappendicitis in a case presenting circumscribed edema, thyroid enlargement, eye signs and cardiac derangement.

The more complex associations were instanced, among others, by:

CASE III. Goiter with asthma; paroxysmal tachycardia; hay fever; emaciation; par-

oxysmal polyuria (apparently hyperacid); subacidity; healed tuberculosis.

CASE XVI. Floating kidney, with renal and other crises; operation; kidney enlarged, capsule adherent; eye signs; nail signs; erythema; circumscribed edema; palpitation; syncope; hemiparesis; gastralgia (not hysteric).

CASE XVIII. Metrorrhagia; erythema; hyperidrosis; glycosuric crisis; eye signs; dermatography; nail signs; hemophilia, gout and diabetes in family.

CASE XIX. Ovarian neuralgia; painful menorrhagia; hay fever; paroxysmal acrocyanosis; relaxation of uterine ligaments; operation; substitutive crises; thyroid enlargement; eye signs; nail signs; anidrosis.

CASE XXV. "Nervous heart"; hemoptysis; angioectasis of tongue, pharynx and epiglottis; enlarged thyroid gland; early pulmonary tuberculosis; chlorosis; dermatography; nail signs; menstrual irregularity; hemophilic and gouty family history.

CASE XXVII. Hemoptysis (from trachea or bronchi?); enlarged thyroid gland; pigmentation; anginoid pain; occasional tachycardia; circumscribed edema with erythema and venous congestion; choreic movements.

CASES XXXII and XXXIII. Incomplete Graves's disease with migraine in one sister, acrocyanosis and menorrhagia in the other. Pulmonary tuberculosis and bleeding hemorrhoids in the brother. All exhibit nail signs, etc. Gouty and tuberculous parents.

CASE XXXIV. Recurrent paronychitis; migraine; circumscribed edema; premenstrual epistaxis; transient pigmentation; transient hemianopsia; tricolored nails; dermatography.

CASE XXVIII. Angiospastic "facial neuralgia" in a patient recovered from exophthalmic goiter; cardiomyopathy; visible distention of temporal artery; relief by nitrites; history of anginoid attacks previously; dermatography; nail signs; cutaneous vascular signs; pigmentations; interesting family history.

Already in 1890 attention had been called to the frequent association of thyroid derangement with the group of symptoms under discussion, and this was again emphasized in the Pan-American communication (1893). As, with the work of Sajous and others upon the endocrins, the intimate relations of the internal secretions with the

involuntary nerves became manifest, a still further extension of the idea seemed justified. In a contribution to the Osler Birthday volume (1919) calling attention especially to the fundamental relations of synergism and antagonism obtaining between this condition and cancer, tuberculosis and diabetes, the term *autonomic-endocrin ataxia* was tentatively suggested. It is not possible, however, always to demonstrate in an individual case either the presence or the nature of the endocrin disturbance, and when recognizably present, one cannot say whether it preceded, followed, or appeared simultaneously with, the other phenomena. Thus, while it is quite probable that some endocrin fault is an integral part of the complex, we cannot dogmatize, and must await further light upon the physiologic relations, not only between the autonomic and endocrin systems in general, but also among the various subdivisions of each system, both with one another, and with special portions of the parallel system.

Until these questions are brought at least within sight of solution, we may, indeed, theoretically consider that autonomic disturbance always involves endocrin derangement, and that endocrin derangement always involves autonomic disturbance, and that either may provoke the other; but we must postpone the definite extension of our nosologic terminology. The limited designation of *ataxia autonómica*—in English, *autonomic imbalance*—is therefore retained in this article.

**PATHOGENESIS.**—Autonomic imbalance, as has been said, is manifested only by certain individuals. It is probably always familial, hereditary and congenital. Although in some instances the condition may seem to have been acquired after a depressing illness, as influenza or typhoid fever, it is reasonable to suppose that the depressing influence has made active a latent hereditary tendency. The fundamental *diagnosis*, as has always been insisted upon, is a recognition of the *peculiar constitution of the patient*; and the naming of the

special collocation of symptoms that he happens to present at any given time is a secondary matter. Thus, the same individual may come under observation at one time with a vasomotor coryza, non-pollenic in origin, at another time with hay fever of which the excitant may be known or discoverable; at another time with migraine or ivy-poisoning, or swellings in and around the joints; or with pseudo-angina (which is not always a "pseudo-diagnosis"), or pylorospasm, or other visceral crisis; or with an erythematous, eczematous or purpuric eruption; or even with angiospastic paralysis or exophthalmic goiter.

In certain cases, indeed, the manifestations may be so varied over a period of years that the patient, applying with each new symptom or syndrome to a different physician, might be fitted with a dozen or more differing diagnoses—each correct enough, perhaps, in respect to the special seizure, but incorrect, or at least incomplete, in respect to the underlying condition. Upon the recognition of that condition, however, the intelligent management of the patient must depend.

As pointed out in the communication to the Pan-American Congress previously referred to, the peculiar individual responses to foods, to drugs, to bacterial invasion, to certain irritants, to meteorologic conditions, to psychic influences, are commonly termed *idiosyncrasies*. But what shall it profit us to translate our ignorance into Greek? Idiosyncrasies must have a physiologic basis.

When such a condition is congenital and apparently inherited, shared with others of the same family, found in



many families of the clan, and in addition manifested in many unrelated families, it is evidently not so purely individual as the term idiosyncrasy would imply, but is representative of a condition actually or potentially present at some time in all men. It is abnormal not *quoad naturam*, but *quoad momentum*. It may be a reversion to a condition formerly common to the race, or may be the beginning of a new development of good or evil promise.

Autonomic imbalance, then, designates not a malady or affection, but a fundamental or constitutional fault, out of which, through the incidence of various exciting and determining causes, varying symptoms and symptom-groups may develop.

*These causes, it must be repeated, not only are inadequate to excite disturbances of like kind or degree in normal persons, but will not invariably excite the same disturbances in different subjects of autonomic imbalance, nor even in the same individual at different times.* Thus, many women use face powder containing orris root, but perhaps only one in hundreds suffers with asthmatic paroxysms in consequence; and that one may at times be free from all disturbances, and at other times have hives or vasomotor coryza instead of bronchial asthma. Many men and women are subjected to eye-strain—but not all have migraine or gastric derangements as a result thereof.

Many children knock against chairs, or are deservedly or undeservedly spanked—but only a few react to such contacts or to gentle correction with the appearance on their bodies of widespread bruises or generalized swelling.

[In one such instance, indeed, unfounded accusations of step-maternal cruelty were brought. The writer has elsewhere discussed the medico-legal aspects of such cases. Their recognition is easy and important.—S. S.-C.]

Many people have to wait for trains or experience other petty annoyances—yet it is not common (whatever may be the case when that which is awaited is a battle, or that which disturbs mentality is an earthquake) for colliquative diarrhea to be so produced; polyuria is perhaps found in a greater number, and is probably experienced by the majority under adequate emotional strain. Thousands of wives failed to hear from their sailor-husbands during the World War, but it could not have been many in whom under the strain a tendency to lip-swelling invaded the larynx, also. All mankind suffers from sufficiently excessive heat or cold—but only a few react with cyanotic skin, digital fissuring, or ulceration to moderate chilling, or with pronounced erythema, blistering, or excessive perspiration to slight rises of atmospheric temperature.

Drugs are taken, with and without good reason, by the majority of human beings—but it is a small proportion of the patients of any one physician that will exhibit such reactions as fever, delirium and scarlatiniform eruption following the administration of 1 grain of quinine sulphate; as swelling of the face and hands upon taking small doses of nux vomica; as catalepsy of nearly two days' duration following the ingestion of  $\frac{1}{2}$  grain of morphine sulphate.

[Second, perhaps third, attacks of scarlatina and measles are conceivably possible, but some instances, so reported, are found

upon investigation to have been scarlatiniform or morbilliform rashes in children, more rarely in adults, the subjects of autonomic imbalance. Provocation in food, drug, fatigue, emotion, can sometimes be traced, as in the child who exhibited the marked "idiosyncrasy" to quinine, and whose brief scarlatiniform seizures were once accompanied with fever. In one case, in a boy of 12, repeated desquamation followed a febrile scarlatiniform erythema. This boy's sister had exophthalmic goiter, and he later developed hay fever; many of his aunts and cousins had other forms of autonomic nerve-disorder.—S. SOLIS-COHEN].

The proverb "One man's meat is another man's poison" is sufficiently ancient; yet knowledge has recently been enlarged as to the wide range of disturbances that may follow the taking of certain foods by certain individuals. These disturbances include not only symptoms referable to the alimentary tract, or such commonly recognized food-sequels as urticaria and migraine, but also asthma, pseudo-angina and epileptiform seizures. Aphasia and amnesia dependent on organic lesion are well known; and that one may be "dumfounded" or "struck speechless" by surprise or other strong emotion is recognized by the existence of such words and phrases. Many persons have had tapeworms. Yet that the horror excited by the discovery of tapeworm segments in the stool should be followed by a transitory amnesia, only to be explained by cerebral angiospasm, is perhaps a unique incident.

Most human beings are at one time or another subjected to alarm, shock, fright, fear; but it is a relatively small number in whom shock or fear crystallizes (to paraphrase Blake's apt characterization) into Graves's syndrome; or who become

transiently hemiopic in consequence. Anger is not rare among men, but only in those who, like John Hunter, have a tendency to coronary spasm may life "be at the mercy of any fool."

[True angina pectoris, or coronary thrombosis, has passed beyond autonomic imbalance to definite lesion; yet either may, in some instances at least, have originated in a functional disturbance, determined to the cardiac arteries or musculature by some tangible change, such as arteriosclerosis, aortitis, etc., or by some more obscure factor.—S. SOLIS-COHEN].

It is needless to multiply examples further; one might fill many pages with them. It may be well in passing, however, to recall the varying susceptibility of hay fever and asthma sufferers. One person suffers from exposure to maize and laughs at timothy or ragweed. Another scorns roses and must flee golden-rod. Another may be immune against roses until his mucosa has been sensitized by a special irritant, and then lose that and other ordinary immunities. But all of the excitants mentioned, and numerous others, have their sneezing, itching, strangling victims, and certain unfortunates seem susceptible to every one of them—or perhaps to develop susceptibility to some in gaining immunity from others.

Three factors, therefore, are seen to be necessary to the development of the various overt symptoms and symptom-groups dependent upon autonomic imbalance:

1. The fundamental liability.
2. An excitant.
3. A local determinant.

The liability is one and constant, the excitants and determinants are various and often inconstant; hence

the variety and the variability of symptoms and syndromes. When inconstant excitants and determinants recur periodically, as with the seasonal pollens that excite hay fever, the attacks are likewise periodical. When these factors present irregularly, the attacks are irregular, as in hives and angioneural arthroses; when they are persistent, the consequent disturbances persist, as in certain derangements of digestion. Often, too, after a transient cause (*e.g.*, fright) has ceased to act, the disturbance it has set up tends to persist in whole or in part, almost indefinitely; and this is especially the case when an endocrin function is involved, as in Graves's syndrome.

*Excitants* may (*a*) arise within the body; (*b*) enter it from without, or (*c*) operate from the environment. They are as numerous and as varied as the factors that constitute the organism and the world about it; they cannot be catalogued. Many of them have been cited, however, by name or type, in the examples given, and those most frequently encountered fall into certain well-recognized groups, as follow: (1) Emotion; (2) fatigue; (3) reflexes; (4) trauma—which may be of the slightest; (5) meteorologic changes, principally thermal and electric; (6) *noxæ*—systemically toxic or locally irritative—(*a*) formed in the body, (*b*) introduced from without, or (*c*) acting upon the external surfaces (skin, mucosæ).

The *emotion* concerned may be pleasurable or painful, exciting or depressing, sudden or long continued, and under the latter head we include, for convenience, prolonged mental strain and anxiety. Shock, fright and fear seem to be more fruitful as provoca-

tives than joy or merriment, although in one patient angioneurotic edema of the tongue and larynx seemed to have been produced by the pleasurable excitement attending a sister's wedding.

Among *noxæ* are included the products of both normal and abnormal metabolism, excessive or perverted secretions, bacteria and bacterial poisons, tissue poisons, pollens, keratins, drugs, foods, etc. The list is interminable. It is also possible that both emotion and fatigue act by means of *noxæ*—as for example, excessive or perverted endocrin agents, metabolic products, tissue poisons. It is also to be noted that there are, so to speak, negative *noxæ*; for example, temporary or permanent deficiency in an endocrin product may render other endosecretions relatively toxic—in other words, set up an endocrin imbalance.

Whether perversions of metabolism and derangements of internal secretions are to be classed only with exciting factors or are concerned in the production of the fundamental liability, or whether there is a vicious cycle which extends beyond individuals into generations, cannot be definitely stated. Doubtless in some cases there is a specific and hereditary anaphylaxis.

That *local determinants* must exist is evident from the fact that not only do different individuals react to the same excitant with symptoms differently localized, but also the same individual, reacting to the same excitant, may present at different times a different localization—as, notoriously, urticaria or asthma. But the determinants are often very difficult to detect. Certain agents (or agencies)—

*e.g.*, heat, cold, trauma, the gouty poison, bacteria, eyestrain—may act both as excitants and determinants, or now as one and now as the other.

Among recognizable determinants, prominence is to be given to the *local incidence* of the excitants just mentioned as playing a double rôle, as also of other irritants, which might not of themselves alone be sufficient to set up disturbance of the character under discussion.

Other factors determining the *locus* or *focus* of disturbance are anatomic peculiarities, such as nasal obstruction, visceral ptoses (these latter being quite common in the subjects of autonomic imbalance), redundancies of the intestine, vascular anomalies; selective tissue affinities; *loci minoris resistentia*, sometimes inherited, sometimes the result of incidents in the personal history of the patient; over-exertion of a part, leading to hyper-excitability, or to exhaustion, central or peripheral; mechanical conditions, such as position (*i.e.*, gravity and pressure); reflex influences, as from eyestrain, already mentioned, or from sources of irritation in the gastro-enteric tract (*e.g.*, undigested food, retained feces, anal fissure, hemorrhoids), or in the respiratory tract (*e.g.*, nasal polypi). Withal, we must often confess to failure to determine the determinant.

In certain irregularly recurring manifestations, with tendencies at times to long continuance, but in which protracted periods of freedom do occur despite the constant presence of the excitants and possibly of the determinants as well (notably, *e.g.*, in certain cases of asthma), it is evident that some *additional factor* or factors must be at work. Many in-

teresting and obscure problems of synthesis in etiology are here involved, and their adequate discussion is impossible. One may think of the general tendencies to rhythmicity in the organic processes, exemplified both in normal and abnormal functioning; as, likewise, of the possibility of plural excitation and plural determination, a necessary factor (or factors) present at one time being absent at another. In the disturbances under consideration anatomic peculiarities, if present, are constant, but bacterial invasion and its results may be necessary, in addition, to determine the symptoms provoked by dust and the like to the bronchial tract; or it may be that in certain instances the respective rôles are reversed, dust acting as a determinant, bacteria or their poisons as excitants. No definite pronouncement can, however, be made.

The *familial and hereditary* character of autonomic imbalance has been stated, but certain features pertaining thereto require brief additional consideration. We may speak of parents and children as a family, and of a group of related families tracing to a common ancestor or to common ancestors, as a clan. The histories published in the Osler Birthday paper, and hundreds of like records, show definitely certain facts concerning the families and clans presenting evidences of autonomic imbalance.

It has been repeatedly emphasized that the special symptoms or symptom-groups presented in the course of life by a given individual of the peculiar constitution described may vary considerably. Still more varied is the symptomatology presented by the larger units of family and clan.

Nevertheless, certain types of disturbances recur with considerable frequency through the life of the individual and through the family and clan histories; thus the physiologic kinship of the various forms of disturbance is as evident as the blood-kinship of the various individuals.

When we look into the other features of the pathologic histories of clans and families, we are struck with the frequency of mention of 2 groups of ailments: (a) Tuberculosis and carcinoma; (b) gout, rheumatism and diabetes. Analysis shows, however, a considerable difference between the relationship of the last named group of ailments and that of the other 2 affections to the autonomic disturbances.

Autonomic ataxia occurs in the *immune individuals* of tuberculous and carcinomatous families and in the *immune families* of tuberculous and carcinomatous clans. Gout, rheumatism and glycosuria or fully developed diabetes, on the contrary, occur in these same individuals or families—those, namely, that exhibit a tendency to be immune from tuberculosis and cancer. In other words, there seems to be an antagonism between the 2 ailment-groups and freedom from one is accompanied with liability to the other. Neither immunity nor liability is, indeed, complete; but the oppositional tendencies are unmistakably evident.

Autonomic imbalance does, indeed, exist without traceable family history of either of the ailment-groups cited. In how far this means absence, and in how far it may merely betoken ignorance, one cannot say. But excluding the negative histories and considering only the positive ones, it

has seemed rational to infer that in such instances the development of autonomic imbalance depends upon an inherited excess of the factors of acquired immunity against tuberculosis or carcinoma, such immunity-inheritance carrying with it, however, a decreased capacity to metabolize carbohydrates, and therefore a liability to ready exhaustion of the pancreatic islet cells.

Just what rôle is to be attributed to the gout-rheumatism tendencies is not clear. That these oppose tuberculosis and carcinoma and favor autonomic neuroses is an old observation. Disappearance—for several generations at least—of the tuberculosis-carcinoma of a clan has, in some family histories, followed intermarriage with a gouty or rheumatic stock; but the number of instances that could be traced through a sufficient number of generations is too small to warrant the tempting conclusion. Still, the possibility that autonomic imbalance may arise in part from the interactions of gouty and tuberculous heredities is worthy of investigation.

That autonomic imbalance is in some measure associated with thyroid-adrenal activities is indicated by many of its phenomena. What may be the relation between these two sets of possibilities is at present a subject of speculation only. In connection with such speculation, the marked recurrences of leukoderma in the history of the tuberculosis-immune families of one tuberculous clan in which a gout-intermarriage is recorded, and of thyroid derangements in another, seem worth the noting.

Hysteria, neurasthenia and epilepsy

are likewise found with considerable frequency in the family histories of the subjects of autonomic imbalance. That there is some significance in this is evident, since they all betoken a somewhat unstable constitution of the nerve system in general. Some of the patients may themselves be hysterical or neurasthenic or hypochondriac, or suffer with *petit mal*, less frequently with *grand mal*. But these make up a very small proportion of the whole, and the symptoms we are discussing are not symptoms of hysteria. Many of the patients are of an unusually high grade of intelligence and mental control; among them are found poets, novelists, playwrights, actors, musicians, teachers, bankers, lawyers, physicians, of reputation and eminence, and women of great social talent. It may be that in these the facility of response of cerebral vessels to stimuli, external and internal, is not devoid of advantage.

**SYMPTOMS.**—From what has been said it is evident that there is no definite symptomatology of autonomic imbalance, but that numerous symptoms of excessive or deficient or aberrant performance of the functions of organic life—and especially those of the heart, the vessels, the secretory glands and the unstriated muscle fibers—may appear in varied association from time to time, according to the incidence of special exciting causes and the presence or occurrence of local determining factors. Some of these symptoms and symptom-groups, as already stated, are not only well recognized but have received special titles, under which they are described and discussed in this volume, as in all textbooks.

Autonomic imbalance is all of them, and none of them. It is the *condition precedent*, without which the exciting and determining causes would fail to produce the special symptoms. As a matter of fact, it is not probable that any one has complete autonomic control; yet equally, as a matter of fact, the vast majority of human beings have control practically adequate to all ordinary occasions.

The symptoms resulting from defective control are, on the whole, phenomena perfectly normal under adequate causation. Their abnormality lies in the fact of their occurrence under stimuli normally inadequate, in their undue persistence, or in their excessive degree. They are also at times characterized by a certain definite associative character.

They may vary much in the same person at different times.

[The same patient may show at one time hives; at another, "dead finger"; at another, acute indigestion, with colic and pyrosis; at another, vertigo or asthma; at another, membranous enteritis. Or eczema may alternate with purpura in the intervals between crises of vomiting or of polyuria. In one case, partial loss of vision—in another, complete loss of vision—was the initial symptom; but the recurrent crises were of angioneurotic edema, affecting especially the lips, tongue, or larynx. The variety, if not infinite, is at least interminable. Sometimes there is an abrupt transition in the type of attacks. Thus, one patient had serous diarrhea, with colic, annually from his 6th or 7th to his 19th year, when hay fever was apparently substituted. Another patient suffered from paroxysmal tic instead of the previously manifested pseudo-angina pectoris. Patients who have had frequent migraine in early life may have, in later life, infrequent headaches, gastro-enteric crises or asthma, instead. Sometimes the substituted crises are modifications of the original type rather than complete departures. In one patient, asthma of

frequent occurrence took the place of hay fever that had appeared every August for 19 years. A patient having attacks of hematuria later suffered from menorrhagia or metrorrhagia instead. In another woman, following oophorectomy, hemicrania, recurring biweekly, was substituted for menstrual sick headache. Most women develop some vasomotor disturbance during the climacteric, but in those belonging to the class under discussion the symptoms are exaggerated and often bizarre.—S. SOLIS-COHEN.]

The symptoms may be manifested in the course of various acute and chronic ailments, tending to confuse the diagnosis if the constitutional tendencies of the patient be not recognized. So also, there may be added to the symptoms dependent on autonomic imbalance secondary disturbances arising from the character of the function primarily disturbed; *e.g.*, thyroid hyperactivity is sometimes excited, with its increased metabolism and other characteristic phenomena.

As a whole, the symptoms arising from autonomic imbalance under appropriate stimuli may be divided into 3 classes: (1) Those characterized by excessive relaxations (dilator-excitation or constrictor-paresis) of vessels and tubes; (2) those characterized by excessive constriction of vessels or tubes (constrictor-excitation or dilator-paresis); (3) those in which phenomena of the 2 opposite groups are commingled. The third class is the most common. When the vasomotor system is especially involved, cardiac inhibition is commonly disturbed also; but there are many cases in which this is not clinically evident. Graves's syndrome presents an extreme type of the phenomena of excessive vascular dilatation, with paresis of cardiac in-

hibition; hence symptoms of this order may be called the Graves type. Raynaud's syndrome presents an excessive type of vascular constriction, and symptoms of this order may be called the Raynaud type.

[Excessive ecto secretions are common accompaniments of the first class; the second class is frequently associated with deficient ecto secretions; but neither association is invariable. So, too, overactivity or subactivity of the thyroid or the adrenal, and disturbance of endocrin balance in general, is frequently present, but cannot be definitely aligned with either group of symptoms. Here, too, the phenomena are commonly "mixed" and careful study of the individual patient and his reactions to endocrin agents is always necessary.—S. SOLIS-COHEN.]

Between these 2 extremes are many varieties, differing much in severity and in locality.

Blanching or marbling of the skin, sometimes deep purplish and blackish discolorations leading to suspicion of gangrene from organic obstruction of vessels, angioneurotic congestions and edemas, petechiæ, varices and even angiomas are the external expressions of similar conditions of the superficial or deeper internal structures. Not only the conjunctiva, retina, nose, lips, mouth, tongue, pharynx, esophagus, cardia and pylorus, rectum, larynx, trachea, bronchi, but also the appendix, gall-ducts, pancreatic ducts, ureters, uterus and other abdominal organs, and even the brain, as shown by Hansell's studies of the ocular fundus, may be the seat of these vascular disturbances, to which, in regions supplied with unstriped muscles—as in the alimentary tract, the bronchi, the ducts—spasmodic obstruction may be added.

As a source of both subjective and

objective phenomena—as a rule paroxysmal, recurrent and painful—such hyperemias and ischemias cannot but be prolific. While the respiratory tract may contribute hemoptysis, hay fever, asthma, to the semeiology of the fundamental disturbance, the skin may offer erythema, urticaria, eczema, purpura, and falling of the hair; the alimentary system, indigestion, nausea and vomiting—sometimes cyclic (and probably of cerebral origin)—colic, membranous enteritis, serous diarrhea, hepatic, pancreatic or appendicular colic, hematemesis, and even gastric or duodenal ulcer; the urinary system, renal colic (but not calculus), glycosuria (from adrenal or pancreatic disturbance), polyuria, albuminuria, hematuria, etc.; the genital system, menstrual and other disorders; the joints, intra-articular and peri-articular swellings commonly mistaken for rheumatism and gout.

[The symptoms of the menopause are essentially symptoms of autonomic—and especially vasomotor—imbalance. But this is a transient phase in the devolution of the female. It gives, however, a diagnostic and therapeutic hint. Arthritis deformans, genuine rheumatic and gouty disorders, like carcinoma and tuberculosis, have an etiologic rather than a symptomatic relationship with the condition.—S. SOLIS-COHEN.]

All regions are subject to angioneurotic edemas, which in the larynx or brain may become threatening to life. Paroxysmal disorders include migraine, of both congestive and ischemic type; pseudo-angina (pectoris and abdominalis); “palpitations,” functional cardiac murmurs, paresthesias, numbness and tingling in various regions, “dead fingers,” tics, tremors, muscular jerking, leg cramps, vertigo—with epileptiform

seizures as an occasional surprise to emphasize the importance of the morbid process.

Disturbances of special sense affect vision chiefly, and are central in origin—probably ischemic,—transient hemianopsia being the most characteristic. Sometimes audition is disturbed, as by recurrent buzzing—with or without accompanying vertigo—or sudden “pistol shot sounds.” These last commonly wake the patient out of sound sleep and may be accompanied by sudden jerking of the limbs and even of the trunk. Anomalies of taste and smell are occasionally met with. Thermal sensation is disturbed subjectively rather than objectively, and more frequently as a general impression of heat or cold than as a local symptom; but localized burning (commonly accompanied by flushing) and localized coldness (commonly accompanied by pallor) do occur.

The blood-pressure is commonly low (*circa* 100 to 110 S., 60 to 80 D.), but may rise markedly during spastic paroxysms, and in rare instances, probably associated with overactivity of the adrenals, the chromaffin system, or the posterior pituitary, may be continuously high. Moderate anemia, with hemolysis, is not uncommon, while in some cases persistent eosinophilia is observed. Erythrocytosis is among the rarest phenomena. Recurrent blood-losses from any or all regions—rising at times to the importance of hemorrhages—are not uncommon.

**DIAGNOSIS.**—The diagnosis is in the main a diagnosis of the patient, rather than of any particular collocation of symptoms presented at a given time. (We refer here to



the diagnosis of autonomic imbalance, and not to the various symptom-groups, which, insofar as they exhibit a consistency of type and have received nosologic designations as asthma, exophthalmic goiter, urticaria, hay fever, etc., are discussed under those heads.) For while subjects of autonomic imbalance present a continuous syndrome (as Graves's or Raynaud's) or what may be termed recurring attacks of a consistent type—*e.g.*, migraine, asthma, urticaria, hay fever, cyclic vomiting, —others present from time to time attacks of varying type; and even those who exhibit recurrences of paroxysms of a consistent type may, in the intervals, have various other kinds of seizures.

That organic affections or acute inflammations are mimicked by vascular crises, and that patients have thus been mistakenly operated upon for appendicitis, hepatic colic, renal colic, etc., has been stated. It must not be forgotten, on the other hand, that repeated vascular disturbances in an organ or system may eventuate in such chronic organic affections as, for example, interstitial nephritis, gastric ulcer, general arteriosclerosis, angina pectoris. In some cases apoplexy has been the terminal event. Thus, mistake is possible in either direction.

As a rule, the paroxysmal (critical) character of the autonomic disorders and the absence of distinctive signs of infectious malady or organic affection will establish the probability of the diagnosis, either positively or by exclusion. It becomes more certain if the patient's family history shows the occurrence of similar or related "spells," and certain *physical charac-*

*teristics and significant reactions* to environment are found to be present. They are not all present at the same time, nor does every case show all of them at any time, while but few of them are present continuously. Nevertheless, every case will show, at one time or another, a sufficient number to be significant. Some of them are the exact opposites of others, indicating the Graves or Raynaud type of phenomena, respectively—as widening of ocular commissures, flushing of skin in the former; narrowing of commissures, blanching of skin in the latter. But, as repeatedly emphasized, the same person may exhibit both types of phenomena, simultaneously or at different times. Hence it has not seemed worth while to make an arbitrary division of cases or signs, based on theoretic possibilities not often presented *in esse*.

The characteristics and reactions of greatest import may be thus summarized in brief catalogue fashion:

**Physical Characteristics and Subjective Phenomena.**—*Skin*: The cutaneous surface exhibits marbling or mottling; dilatation of superficial vessels; petechiæ; angiomas; telangiectases; pigmented spots; papillary, often pigmented, excrescences; tattooed appearances, coming on especially on exposure of the naked body to cold; massive congestion of dependent parts, especially the hands, which may be pink, red, leaden, blue, purple, or variously mottled. The fingertips are often enlarged; the nails may be curved, bi-colored or tri-colored, darker at the base and exhibiting a deep red line near the fingertip. The skin about the nail base is often thickened and brick red. The palms may be hot or cold, and are

often moist, even clammy. There may be excessive sweating, or, less commonly, scantiness of perspiration, even in summer. Bromidrosis is sometimes met with.

*Eyes:* The eyes are often staring; the commissures are widened. Retraction of upper or lower lid, or both, may be unilateral or bilateral, constant or intermittent, or developed on excitement or at command, as by having the patient converge on a relatively near object (the physician's upheld finger) and open the eyes widely. Tremulousness of the lids on light closure, interrupted (jerky) descent of the upper lid (hitch); v. Graefe's and v. Stellwag's signs; paroxysmal winking, etc., may be shown even when there is no suspicion of Graves's syndrome. Pigmentation of and around the lids may be marked.

Rarely, drooping lids or narrowed (squinting) commissure is seen. Dilatation or inequality of the pupils may be constant or intermittent; the pupil may dilate and contract irregularly under stimulus of light or accommodation. Nystagmus is not rare. Distention and tortuosity of retinal vessels without sclerosis is common; spastic contraction of retinal vessels is less frequently observed.

*Thyroid Gland:* Excluding the developed Graves's syndrome, the thyroid, as a rule, is moderately or slightly enlarged, but quite soft. The enlargement may be intermittent. The gland is rarely atrophic.

*Heart and Vessels:* The heart is easily disturbed. Palpitation is common. Tachycardia or bradycardia may be of frequent or infrequent recurrence, or the pulse may be con-

tinuously much faster or much slower than the ordinary person's. Functional arrhythmia may recur more or less frequently. Blood-pressure is commonly low. Functional murmurs are frequent; organic affections may be present incidentally or essentially.

*Urine:* Slight albuminuria with or without infrequent casts is common; hematuria is relatively infrequent, but hemoglobin and red cells are not infrequently found on microscopic, chemical, or spectroscopic study, when blood or blood-pigment is not obvious to the naked eye.

**Chief Tests.**—*Dermographism*, either ischemic, hyperemic or mixed, *factitious urticaria*, and local or general pilomotor reflex are easily elicited, as is also *blushing*.

*Silver* leaves a bluish-black or brown mark when drawn over the skin of face or breast. (Black mark referable to soap, talc or zinc oxide face powder must be excluded.)

*Hot water* intensifies redness of the extremities, while *ice-cold* water may change blueness (cyanosis) to redness (hyperemia) in the immersed member, the parallel non-immersed member being made deeply cyanotic. Sometimes ice-cold water produces blackness of the nails.

In *dilatative* (Graves's type) cases a cyanotic member (*e.g.*, hand) if *stroked* or *elevated* becomes pallid, and when stroking is stopped or it is again depressed, changes from white to pink, to red, to purple, to blue, as the blood returns first to capillaries, then to venules, then to veins. In *spastic* cases (Raynaud type) the stroking or gravity has little effect.

Excessive reactions to pilocarpine, on the one hand, or adrenalin or atropine, on the other, are considered

by Eppinger and Hess to establish the diagnosis of vagotonia and sympathicotonia, respectively; but both classes of reaction may be exhibited by the same patient.

Having determined the constitution of the patient, it is important, of course, by study of his habits and environment, by cutaneous sensitization tests, and by all other available means, to discover the special excitant or excitants to which he is susceptible, and the factor or factors that determine the diffusion or localization of the symptom.

**TREATMENT.**—Treatment is *preventive*, *palliative* and *remedial*. Each case is a problem unto itself and calls for individual study.

The *preventive treatment* is practically the same for the Graves, the Raynaud, and the mixed types. It is the treatment of autonomic imbalance.

*Palliative treatment* is necessarily symptomatic, but with consideration of the underlying disorder. It differs with the specific phenomena presented, and may be termed the treatment of Raynaud's or Graves's syndrome, of erythromelalgia, of visceral angioneuroses, of migraine, of asthma, of hay fever, of angioneural arthrosis, of urticaria, etc. (*q.v.*).

*Remedial treatment* involves both measures appropriate to the special syndrome presented and general measures from the preventive category.

Here is to be taken up the preventive and general remedial treatment; special symptom-groups and their management are considered elsewhere.

Preventive and remedial measures must be in a measure adapted to the

condition of erethism or of apathism manifested at the time or in general, being thus designed to soothe, to control, or to stimulate, as may be required. In most patients, however, we find a commingling of both orders, an inconstancy, a tendency to variation, that can only be termed incoördinate, and it is to the establishment and maintenance of equilibrium, to the reinforcement of central control, that treatment must especially be directed.

Erethistic symptoms call for **rest**, general or local, complete or partial, psychic as well as physical; for the soothing measures of physiologic therapy, and for **sedative medication**. Apathetic symptoms call for **exercise**, perhaps **massage**, and for **tonic and stimulating physiologic measures and medicines**. Apparent overaction may, however, be a sign of irritable weakness, and stimulating and tonic measures thus be required in erethistic cases also, to alternate with or to supplement those of sedation. So, too, even in generally apathetic cases some functions may lack sufficient inhibitive control, and **rest** or **sedation**, or both, be necessary. Once more we find *restoration of balance* the important object and individual case-analysis imperative.

There are certain *general measures*, however, that apply to all cases.

Emotional disturbance (which is sometimes sexual), special noxæ, fatigue, trauma, latent and focal infections as sources of toxemia, and other recognized **excitants** are to be **avoided** or **guarded against**. **Desensitization** and **bacterination** here find place. **Secretions** and **excretions** are to be **kept free**. **Diet** must be regulated.

Important supplemental measures are **correction of eyestrain** and of **anatomical maladjustments**, such as visceral ptoses, uterine displacements, etc.; the prevention of autotoxis, not only by regulated **diet**, but also by **gastric lavage**, perhaps **colon flushing**; by occasional **purgation** with **calomel** as the main agent, or the rather continuous use of some such mild laxative as **sodium phosphate** or a mild saline water, and by the use of **lactic acid bacilli**, **methenamine**, **phenyl salicylate**, **betanaphthol**, **guaiacal carbonate** and the like, as intestinal antiseptics.

Judicious **exercise**, which may take the form of walking, riding, moderate golfing, etc., is necessary, even in cases in which it may have to be alternated with rest—that is, of course, if we exclude fully developed Graves's phenomena. **Massage** may be added or, in some cases, substituted.

The cardiovascular tone, enfeebled by aberrant stimuli, must be enhanced. **Hydrotherapeutic procedures** involving alternate stimulation with heat and cold, together with **friction**—very gentle at first, then more vigorous—are the best measures at command and the easiest of application. The patient is told to follow a simple routine every morning on arising. First the head and neck are to be laved with **cold water**. The whole body below the clavicle is then to be **sponged or sprayed** for 2 or 3 minutes with **hot water** (not tepid); the temperature at first to be merely comfortable, but later, as hot as can be borne. Then the whole body is to be sponged or sprayed for 3 to 5 minutes with water as cold as can be borne, and at the same time, rubbed briskly; or the cold water may be

taken in the hand, and thus rubbed on the body. Drying by rubbing with a coarse (Turkish) towel concludes the treatment. **Showers** may be used instead of sprays, or more elaborate procedures prescribed; but the simplest method is as good as any.

The exact degree of heat and cold varies with the individual, the weather, and other conditions. For **cold applications**, the water may commonly be used as it comes from the spigot; for **hot ones**, spigot water may have to be modified. The patient must judge by his sensations, and is to be encouraged, even in cold weather, to use water as cold as can be borne, and even in hot weather, to use it as hot as can be borne. Following the cold application there should be good reaction, with general flushing and a pleasant sensation of warmth; otherwise the procedure will need modification. The tendency to reaction, having once been initiated, will become more and more firmly established; and the treatment is to be continued during the patient's life. It is both remedial and preventive.

Cardiac palpitation or tachycardia<sup>42</sup> is sometimes troublesome, even in the absence of distinct Graves's phenomena. The patient should **rest**, and a **precordial coil**, first with **hot** and then with **cold** water, or **hot compresses** followed by an **ice-bag**, be applied over the precordium for such time as may be indicated by the severity of the symptoms and the effect of the remedy.

**Electric applications** of various kinds are useful. Apart from special procedures depending on special symptoms, a general toning of the autonomic system seems to follow

persistent **sinusoidal-galvano-faradization** in the region of the 7th cervical and first dorsal vertebræ. The applications are made daily at first, then on alternate days, and so on, with gradually increasing intervals, until perhaps reduced to once in a fortnight, or once a month. In some cases it may be advisable to continue the monthly applications for a year or more, to minimize or prevent relapse and recurrences. Other modalities to be employed under special conditions are **faradization of the stomach** in cases of deficient motor and secretory function and in cases presenting angioectatic phenomena; **galvanization of the cervical sympathetic**; the **static breeze**; the **wave current**; **high frequency discharges** from a Oudin resonator, to the spine, the neck, and the thyroid gland.

**Autocondensation**, labile applications of the **high frequency vacuum electrode**, and **diathermy** are of great value in cases with tendency to angiospasm. **Iodic ionization** of affected parts is useful in joint affections, scleroderma, etc. **Massage**, general and local, and **intermittent pressure** upon the muscles around the spinal column can also be employed with good results in selected cases of all types.

Medication is indicated by the chief special symptoms. Since subjects of autonomic imbalance exhibit many "drug idiosyncrasies," inquiry is necessary before prescribing; especially does this apply to calomel, to quinine, to belladonna or atropine and the mydriatic alkaloids in general, to cocaine, to morphine and to the synthetics of the coal-tar series.

In cases associated with persistently low blood-pressure and an un-

due tendency to vascular relaxation, **adrenal**, **posterior pituitary** and **thymus** preparations, **digitalis**, **sparteine**, **strophanthus**, **cactus**, **ephedrine**, **caffeine**, **cocaine**, **quinine hydrobromide**, **ergotin** and **barium chloride** exemplify the type of agents most commonly useful.

When muscular tremors are important symptoms, **calcium** salts, especially the **bromide** and the **hypophosphite**, with **parathyroid gland**, are indicated. When persistent coryza, excessive sweating, or profuse salivation calls for remedy, **atropine** is commonly the best drug—but in certain instances it fails. Very frequently, in such cases, minute doses of **pilocarpine hydrochloride** ( $\frac{1}{12}$  to  $\frac{1}{8}$  milligram— $\frac{1}{750}$  to  $\frac{1}{500}$  grain), given hourly for a few days in succession, will control the symptom. The drug may then be continued with less frequent doses, or intermitted, according to results.

When there is constriction of the arterioles, especially in cases with high blood-pressure, or when the heart manifestly labors to overcome the peripheral opposition, the **nitrite** group (including **erythrol tetranitrate** and inhalations of **amyl nitrite** in emergencies) and the **papaverine** or **benzyl ester** group are indicated, with the **iodides** and **thyroid gland** to aid in relaxing the contracted peripheral arteries and **crataegus** to sustain the effect. **Aconite** is useful in selected cases; and in crises, as of angina, intermittent claudication and recurrent pulmonary edema, the use of **morphine** may be imperative. **Picrotoxin** as a central stimulant may be useful in all cases, but especially in those (the most frequent) showing *mixed* phenomena, and par-

ticularly when the gastroenteric functions are deranged.

**Surgical Measures.**—The question of surgical procedure is sometimes important, both positively and negatively. In the majority of instances, recognition of the functional basis of symptoms will negative it. On the other hand, exploration or operation may be undertaken not merely through mistake in diagnosis, but deliberately, to settle the diagnostic question, or even as the only possible therapeutic procedure. It is fully justified. In laryngeal or laryngo-tracheal edema, for example, **tracheotomy** or **incision through the cricothyroid membrane** might have to be done as an emergency procedure with scissors or penknife and perhaps a hairpin be used to keep the wound open, in the absence of a cannula. A deliberate procedure with the best surgical technic is, of course, much to be preferred. Instances are known in which death has occurred because such prophylactic tracheotomy was refused or neglected.

While autonomic visceral crises may be mistaken for organic lesion, it is also possible that an angioneurotic patient may have inflammation of the appendix or of the gall-bladder, gall-stones or renal calculus, duodenal or gastric ulcer, and it is much better to operate and discover edema (cases in which angioneurotic edema was demonstrated at the time of operation are on record), or even to "find nothing" than to neglect to operate in a case demanding surgical relief. Moreover, as Osler pointed out, even when the diagnosis is clear, the results of delayed circulation, or of hemorrhage and other events involved in, or following upon, a vis-

ceral crisis of the character described may be such as only surgical measures can properly deal with.

In the writer's experience, half a dozen persons exhibiting unmistakable signs of autonomic imbalance, yet in whom organic lesion could not be positively excluded, have been operated upon by his advice, and neither inflammation nor calculus found. Yet he has not regretted that advice in any instance. Four were cases resembling appendicitis; one was a biliary crisis, and one a renal crisis. In each instance the patient made an uneventful recovery and was not thereafter troubled with a return of symptoms.

It is almost certain that in such instances the change wrought by the operation in local circulatory conditions, and perhaps the severance of nerve fibers, brings about the disappearance of the local determining factors.

In other cases, possibly a dozen or more, the late history of the patients, 10, 20, in one instance 30 years after the first examination, has indicated the development of organic lesion upon the basis of previous autonomic imbalance; and such procedures as dilatation of the ureters or the cardia, gastroenterostomy, uterine curettage, or radiumization, etc., advised by the surgeons consulted, have been concurred in as appropriate to the *status præsens*.

SOLOMON SOLIS-COHEN,  
Philadelphia.

**AVIATORS' SICKNESS** designates the disturbances experienced by aviators owing to the rapid changes of altitude which flying entails.

**SYMPTOMS.**—The symptom-complex of this disorder has been clearly described

by M. G. Ferry, medical officer of a French aviation camp, after a large number of personal ascents in various types of airplanes (*Presse médicale*, January 6, 1916). He states that during ascent, the rapid or slow adaptation of the body—according to the speed—of the organism to the surrounding medium is attended by various physiological disorders varying with the altitude. These, often insignificant and transitory, have in great part escaped the notice of aviators. Headache frequently appears on reaching beyond an altitude of 2000 meters; tinnitus aurium at the same altitude—especially when the motor is placed behind the seat, or when it is not rotary; increasing difficulty of inspiration—associated with augmented facility of expiration in the rarefied air; rapidity and tenuity of the pulse, according to the increase of altitude reached.

Those various unpleasant sensations seem to decrease slightly on assuming the horizontal plane at the highest altitude attained. When, however, any disturbing incidents occur, such as eddying currents, slight repetition of the respiratory or cardiac troubles supervene—of emotional or reflex nature,—which, however, soon subside.

Tests in the rotating chair showed that in fit pilots, particularly those accomplished in aerial acrobatics, rotation produces but little effect on the pulse-rate or arterial pressures. In cases subject to vertigo, nausea, or vomiting, rotation produces a marked rise in pulse-rate and in systolic and diastolic pressures. In subjects liable to fainting, it produces a characteristic fall in the diastolic pressure. In highly strung subjects, liable to develop an anxiety neurosis, there is a marked anticipatory rise of pulse-rate and systolic pressure prior to rotation, which may or may not be further affected by rotation. In subjects who are not incommoded by aerial acrobatics the ocular muscle balance is not affected, whereas in those who suffer from giddiness and nausea this is markedly affected. A falling away of stability of the centers controlling the respiration and circulation is one of the earliest, perhaps the earliest, sign of deviation

from true physical fitness for flying duties. M. Flack (*Lancet*, Oct. 10, 1925).

The descent is attended by sensations more sharply defined in proportion to the velocity and the degree of agitation. The headache disappears—but at an altitude somewhat below that of its original onset. The respiratory movements return by degrees to their normal rhythm, the pulse becomes slower with a more vigorous stroke—although more gradually. Tinnitus aurium, however, subsides but slightly and persists even after reaching the ground for a period which varies with the form and location of the motor—3 to 4 hours when the motors are fixed at the back;  $\frac{1}{2}$  to 1 hour when the rotary apparatus is placed in front of the aviator. An auriculo-tympanic shock is also produced by the act of deglutition during descent, which results from the abrupt re-establishment of equality of pressure on the 2 faces of the tympanic membrane. The painful sensation of throbbing strokes which synchronise with the pulse ceases, while the hearing is improved. When the descent is carried out in short spirals with steep grades, the machine being sharply inclined, palpitation, possibly of emotional origin, sometimes appears. Swooning of short duration may follow. A distinct nervous excitation also follows the landing, manifested in tremor of the extremities and muscular twitchings, slight incoördination of movements, brief periods of palpitation, local congestions of the face, an intense desire to urinate (often unjustified by bladder distention), and increased appetite. All these manifestations soon disappear and are replaced by fatigue and an imperative need of sleep. Some experience severe headache, which is usually also relieved by deep sleep.

Combats between aviators generally occur at altitudes between 4000 and 5000 meters, with the barometer at 47 to 41 cm. The temperature descends by  $1^{\circ}$  C. for every rise of 110 meters at the lower altitudes and for every 200 meters at high altitudes. During an ascent general lassitude may be experienced as a result of the reduction in atmospheric pressure. In full flight, at about 5000 meters,

the aviator may experience pain in the ears, heaviness of the head, somnolence, general fatigue, and apathy. During the descent there may be renewed pain in the ears and tinnitus. Upon alighting there may be temporary deafness and at times a staggering gait. Otoscopy then shows congestion of the entire auditory apparatus. The ear disturbances are due in particular to differences in atmospheric pressure. Hence the relief secured during ascent by Valsalva's method, and during descent, by that of Toynbee. A. Castex (Bull. de l'Acad. de Méd., June 25, 1918).

**ETIOLOGY.**—The disturbances are the result of the rarefied air, and are the same as those experienced by mountain climbers, owing to the low barometric pressure, according to Aggazzotti (Riforma Medica, Apr. 27, 1918). Acute pain in the normal ear is not a direct symptom from this cause, but is indirectly due to it. The conditions producing it are corrected by making swallowing movements, working the jaws, and yawning. There may be minute bleeding from the superficial vessels in lips and nasal mucosa, but the cold prevents extensive hemorrhage, and such has never been observed.

He accepts Mosso's explanation of the disturbances in rarefied air as due to changes in the gases of the blood, especially impoverishment of oxygen and of carbon dioxide. The proof of this assumption is provided by the absence of these disturbances, even in extremely rarefied air, if the blood is kept supplied with oxygen and carbon dioxide. In experiments at the Institute of Physiology at Turin, he was able to bear perfectly a barometric pressure of 140 mm.—which corresponds to an altitude of 13,491 meters—when he breathed a gas mixture consisting of 67 per cent. oxygen and 12.7 per cent. carbon dioxide. He used in this way 11 liters of the mixture, breathing naturally, without the slightest disturbance of any kind. With a mixture consisting of 67.8 per cent. oxygen and 13.4 per cent. carbon dioxide he found that all was well with him even at a barometric pressure of only 122 mm., corresponding to 14,589

meters. The pressures of higher altitudes than this had never been reached in the pneumatic cabinet. His mind was clear, vision normal, his movements certain, with no tremor of the lips or sensation of heat in the face.

When aviators begin to feel disturbances from the rarefaction of the air, they should make muscular movements; this will improve the oxygenation of the blood, since respiration will become more active, and carbon dioxide will be produced in the muscles and pass into the blood.

**PATHOLOGY.**—In a large proportion of mysterious crashes to earth, the cause, according to Surgeon Panter (Jour. Royal Naval Med. Service, Jan., 1918), is loss of consciousness by the pilot. He has had at least 4 cases of pilots completely losing consciousness in the air. Two of these "crashed" on trying to land, which apparently they did subconsciously, without severe injury to themselves, the other 2 both lost consciousness at a height, subsequently regaining it, and were able to recover control of the machine and make safe landings, both feeling extremely ill. He has often noticed how greatly any alimentary disturbance becomes exaggerated in the air, and several cases of vomiting while flying have occurred apart from vestibular vomiting experienced by some pilots on extremely "bumpy" days. In these cases also the pilot, on questioning, has admitted having had slight indigestion before going up. A common cold when accompanied by much nasal catarrh will often give rise to great trouble at a height, and especially during rapid diving, and several times pilots with this condition have come for advice wishing to ascribe their symptoms to a "lack of oxygen," but with the curing of the cold the trouble ceases. For efficiency in the air, robust health is essential. Any minor disability becomes greatly accentuated when the general nervous system is at high tension, as during flight, and there is not the slightest doubt that many "crashes" and "nervous breakdowns" could be averted if all minor maladies were taken in time and brought under treatment.

The influence of flying on the blood was studied by Kaulen (Deut. med. Woch., Dec. 13, 1917). He found that aviation



produces an increase of red blood-corpuscles and of the percentage of hemoglobin. This is distinctly noticeable after 3 months of aviation and is not due to a concentration of the blood from greater viscosity. The leucocytes do not follow a parallel increase. The phenomenon does not occur during a single ascension. This multiplication of the red blood cells is not accompanied by the appearance of nucleated cells, but polychromatophiles may appear. The blood of rabbits and mice carried in the aeroplanes was found to offer similar changes to those met with in man.

**PROPHYLAXIS.**—The prevention or at least mitigation of the disorders incident upon aviation is closely associated with the absence of all physical defects in the aviator. As urged by J. C. McWalter (*Med. Press*, Aug. 21, 1918), of the British Medical Flying Board, whose observations accurately summarize those of other medical officers, the physical qualifications of a flying officer become higher every day. Men who can fly with ease at 5000 or 6000 feet may be useless for some modern conditions of warfare where machines are worthless unless they can fly at 15,000 to 20,000 feet or more. Troubles due to extreme cold, or to atmospheric rarefaction at great heights, may be minimized by the use of oxygen and of warm clothing, but a marvellously elastic vascular mechanism is required before a man can descend with impunity, and in a few minutes, from a height of 20,000 feet. The cardiac muscle must also be in a very healthy state in order to respond promptly to the strain on the circulation. The lungs and bronchial membranes must be not only sound, but proof against the irritation engendered by the heat and smoke of the engine or by the varying moisture of the air. All this means that a man must be young, athletic, fit, sound and strong.

A flying man may have all these qualifications and yet be defective. In actual practice, the author found that of men who have been passed as fit into the Flying Corps, whether by special medical boards or by ordinary medical officers, that gross lesions of the heart, lungs or abdominal organs are seldom present, but that notable defects often exist in the

nervous system, or in the ear or nose, less often in the eyes or throat.

The most usual—but the most dangerous, defect is some disease of the labyrinth. This is often overlooked, being unlikely, in its milder forms, to cause any acute trouble until the patient has mounted some thousands of feet; it then gives rise not only to vertigo and giddiness, but to a lack of that sense of equilibration and location which is of the essence of the successful flying man. One has also found that those flying men who experience most difficulty in judging of the distance of the ground when approaching a landing place, are frequently the subjects of this disorder.

The whole series of rhinological ailments, stenosis, sinusitis, hypertrophy of the turbinated bones, Eustachian tube troubles, even pharyngitis and tonsillitis—all render, in greater or less degree, a man unfit to fly.

Emphasizing the importance of cardiovascular disturbances as a cause of aviation accidents, the writer states that high altitudes may induce unconsciousness through additional diminution of blood-pressure in subjects already suffering from low tension, due to cardiovascular disease. The aviator with initially low pressure is likewise threatened with syncope when the pressure drops too rapidly, and this probably accounts for the sudden falls to death of numerous aviators. The blood-pressure of all aviators should be tested periodically, with special examination of those who report nervous disturbances, dyspnea while in flight, or who have hepatic trouble. An aviator with a diastolic pressure of 60 (Pachon) or below should be considered temporarily disqualified for the work. D. Berthier (*Bull. de l'Acad. de méd.*, Sept. 10, 1918).

The importance of perfect vision has been emphasized by Naval Surgeon H. G. Anderson (*Lancet*, Mar. 16, 1918). He holds that the aviator should have unaided normal vision in each eye separately, and normal color perception. In the writer's experience, which includes much actual flying, the vision had more to do

with determination of position in space than any other sense. Those with defective vision are at a great *disadvantage* in an aerial flight on making landing. The presence of heterophoria, or latent squint, has also been found a cause for making bad landings. Concealed hypermetropia should cause rejection if sufficient to enable a candidate to read 6/9 each eye, with a plus 2 lens. *The importance of perfect color perception is very great.* Its use comes in picking out the color or markings of hostile machines, in recognizing signal lights, and in judging the nature of landing grounds. Night blindness is important in selecting pilots for night bombing. Night blindness is tested by reading ordinary test cards under increased or decreased illumination.

A curious feature to which the same writer calls attention is the fact that it has been found in a fog that it is almost impossible to detect any deviations of position during a flight. Aviators have come out of dark clouds or fogs and found themselves flying one wing down, or even upside down, without knowing it. Therefore most of the impressions which control balance in flying come from the eyes. He advises a thorough investigation into the candidate's equilibrium, muscle sense, and vestibular reaction. In addition to those tests, the psychomotive reactions should be thoroughly gone into, and the aviator should possess a normal reaction time with regard to vision, hearing, and touch.

Results of over 1000 observations in the aviation tests for equilibration by means of the American modification of the Bárány chair (see article on INTERNAL EAR, in the fifth volume), and a collaborative determination of the corresponding pulse rate. Taking the general average it can be said that in 100 cases the stimulation to the vestibular portion of the eighth cranial nerve end-organ by 50 revolutions, at varying rates of speed, produced an increase in the rate of heart action of 9 beats per minute. Babcock (Boston Med. and Surg. Jour., Dec. 13, 1917).

Recently, in Italy, Colonel Gradenigo stated that he considered it was sufficient to test only for nystagmus

and not for pastpointing and falling, because a normal nystagmus alone showed that the internal ears were normal. The reason the other tests were made in America, however, was due to the realization that it was not an end organ alone that was being dealt with, but with a test of a large portion of the central nervous system, most particularly the cerebellum. It had been observed by many fliers that one instructor flew in a peculiar way; he would allow either one wing or the other to be tilted to a dangerous degree without making any effort to correct it. This was true when he was at a high altitude and also at a low altitude; but on nearing the ground, when he could orient himself by the sense of sight, he would straighten out and land satisfactorily. On one occasion he was flying over Philadelphia and entered a cloud; his passenger was an experienced aviator who became alarmed at the manner in which the plane was being guided. This passenger could detect deviations in position which apparently meant nothing to the pilot and which resulted in a dangerous sideslip. Examination in the turning chair on the following day showed that the pilot had practically no responses in nystagmus, vertigo, pastpointing, and falling whereas the passenger showed entirely normal responses. I. H. Jones (Trans. N. Y. Neurol. Soc.; N. Y. Med. Jour., Jan. 11, 1919).

Finally, as emphasized by Bernard (Progrès Médical, May 11, 1918), aviators should constantly be objects of study, the task of the physician being almost exclusively towards lines of prophylaxis. Even when aviators are fitted for the service, surveillance should be incessant. He should live among them, watch the physical and moral modifications induced by flying, study each accident minutely to learn how such can be avoided. The training camp should have a commission for study of these problems, including a physiologist, a physician, a surgeon, an ophthalmologist, a neurologist and an ear, nose and throat specialist. S.

**AZOTEMIA.**—This term refers to the presence of nitrogenous compounds in the blood, particularly when in excess. It is practically synonymous with uremia, which, however, refers more comprehensively to the sum of the toxic manifestations of failure of the renal function in the later stages of nephritis. The proportion of urea in the blood is frequently taken as an index of the degree of accumulation of effete nitrogenous matter.

With reference to the maximum amount of nitrogenous accumulation compatible with normal bodily function, Hérouin states that he has never observed a patient capable of leading an active life when there was more than 2 Gm. per liter of urea in the blood. He maintains that the urea itself has a toxic action. The sodium hypobromite test, however, shows not only the urea, but all the other compounds analogous to it generated through the reaction to the toxic action of the urea and otherwise. The xanthidrol test, on the other hand, shows only the urea, independently of the other compounds.

Hewlett, Gilbert and Wickett found that by giving about 100 Gm. of urea *by mouth* over a short interval of time it is possible to increase the concentration of urea in the blood of normal persons to levels of from 160 to 245 mgm. per 100 c.c. At such levels of blood urea definite symptoms occur, consisting of headache, dizziness, apathy, drowsiness, weakness and fatigue. These symptoms are comparable to those encountered in the asthenic type of uremia.

A change from a mainly carbohydrate to a protein-fat *diet* was accompanied, in the investigations of Addis and Watanabe, by an increase of from 58 to 250 per cent. in blood urea concentration. On a constant diet a variation of from 0.0156 to 0.0438 Gm. urea per 100 c.c. of blood was found; differences in the rate of protein katabolism are the principal causes of this variation. Although, normally, whenever there is an increase in the rate of entrance of urea from the tissues into the blood, an increase in the rate of urea excretion occurs, it is not sufficient to prevent some rise in the blood urea concentration. Permanent individual peculiarities play no part, according to these observers, as a cause of variation

in the blood urea concentration of different normal persons. In a group of 22 subjects, a variation of from 0.0225 to 0.06 Gm. urea per 100 c.c. of blood was found in a series of 106 estimations carried out in the morning before breakfast.

The selective action of the kidneys normally holds the *urea nitrogen* at the level of about 50 per cent. of the total *non-protein nitrogen*. But when the renal function is impaired, urea retention may be very high.

Kast and Wardell found that of 244 hospital patients with a urea nitrogen below 35 mgm. per 100 c.c., 84 per cent. had a urea concentration of not more than 20 mgm. per 100 c.c. Of these 206 cases (the 84 per cent.), only 40 per cent. showed other evidence of renal impairment, while of the other 38 cases, 77 per cent. showed such other evidence. Blood urea estimation is a satisfactory index of renal functioning power; 20 mgm. may be taken as the upper normal limit of urea in the blood of hospital patients.

In some instances, in nephritis, elimination of excess nitrogen is normal, in others it is delayed, and in others still, nitrogen may be almost wholly retained in the system.

Widal has formulated the following *prognostic suggestions* relating to the *blood urea findings*: 0.5 to 1 Gm. per liter, prognosis serious, but prolonged survival possible; 1 to 2 Gm., life rarely continues more than a year; 2 to 3 Gm., survival for a few weeks or months; over 3 Gm., probable survival for a few hours or days. These prognostic indications apply only where the findings referred to are persistent; in more acute disturbances, high blood urea may set in and pass off quickly.

In analyses of blood and saliva, representing various pathologic conditions, the urea content of the *saliva* was found to average 89.4 per cent. of that of the blood. Salivary urea determinations may be used in determining renal functional activity where for any reason it is impracticable to obtain blood specimens. H. W. Schmitz (Jour. of Lab. and Clin. Med., Nov., 1922).

There is a relationship between , azotemia and reduction of the body

temperature. In animals, injection or ingestion of urea in large amounts has likewise been found to cause *hypothermia*. The writer thinks urea has a direct toxic action in uremia. Mozer (Ann. de m  d., June, 1924).

Case of typhoid fever and nephritis in which the retention of nitrogen in the blood due to the nephritis caused reduction of the patient's fever. Lemierre and Bernard (Bull. Soc. m  d. des h  p. de Paris, July 4, 1924).

A relationship to heart disorder has been pointed out by Esmein and Heitz, who

tabulated 25 cases of *pulsus alternans* showing a high blood urea content, from 0.43 to 1.66 Gm. per liter. When the intake of meats was restricted, marked improvement followed. Their experience emphasized the need of placing patients with *pulsus alternans* on a **nitrogen-poor diet** in addition to the use of **heart tonics** and **diuretics**. The alternating pulse, as these authors state, is a sign of heart weakness, and this, in turn, may entail oliguria and secondary azotemia even when the kidneys are sound. Heart tonics may change the whole clinical picture. S.

## B

### BACILLUS ACIDOPHILUS.---

This micro-organism, which is one of the chief inhabitants of the intestine of nursing infants, has been brought into use for the relief of constipation and other disturbances of the intestinal tract. It is described as a strictly non-fermentative and non-putrefactive organism which elaborates no toxic products and differs from *B. bulgaricus* in that it is capable of rapid growth in the human intestine. After infancy it gradually becomes replaced in the bowel by other less benign bacteria; hence the attempt to improve the intestinal flora by implanting it and allowing it to supersede other bacteria present. Its proliferation is stimulated by simultaneous ingestion of lactose or dextrin.

**ADMINISTRATION.**—According to Rettger and Cheplin, acidophilus tablets or powders are of no therapeutic utility, whether taken as such or used to make acidophilus milk. The living, 24 hour milk culture of the organism is the correct preparation for clinical use. For best results Bass and Jones advise that acidophilus milk be taken with the meals, preferably a glass with each meal, in order to inoculate the food heavily with viable bacilli. The daily amount required is 1 pint to 1 quart. With this procedure marked bacterial transformation of the feces is effected in 4 to 10 days, with decrease or even practical disappearance of all other bacteria, which result is generally maintained as long as the acidophilus milk is continued.

**THERAPEUTICS.**—*Bacillus acidophilus* has been used by various observers with favorable results in **chronic constipation** with symptoms of **autointoxication**; **chronic diarrhea** following bacillary dysentery; **mucous colitis**; **sprue**, and **eczema**. Diarrheal cases that could tolerate no other food retained the acidophilus milk.

In 30 cases of **constipation**, Kopeloff used it with good results. In all but 2 cases the number of defecations was increased. In severe cases, as much as 1500 c.c. may be required; with this 400 Gm. of lactose may with advantage be given daily. High enemas of warm acidophilus milk are also effective. Benefit usually persisted a long time after cessation of treatment; in some cases 11 months. When the defecations tended to decrease, continued use of lactose proved beneficial. Transformation of the flora from proteolytic to aciduric may generally be induced by the treatment, and is usually accompanied by almost daily defecations.

In cases of **toxemia** and **stasis** with various symptoms, Mitzell obtained relief in 60 per cent., and in patients with **stasis** and **colitis**, without toxemia, in 80 per cent.

According to Bassler and Lutz, the effects are obtained as well by merely giving several teaspoonfuls of lactose a day, thus stimulating growth of the *B. acidophilus* naturally present in the intestine. It is generally recognized, however, that acidophilus milk in full quantities acts more rapidly. S.

**BACTERIAL VACCINES.—**

Bacterial vaccines are preparations of bacteria, or of their products, for prophylactic or therapeutic use. In the usual liquid form the vaccines are clear, slightly opalescent, or milky, the appearance depending upon the amount of bacterial substance in them. There may be sedimentation. A small percentage of an antiseptic (phenol, tricresol, or liquor cresolis comp.) is added to fluid preparations as a preservative. The vaccine usually contains the whole bacterial cell treated by exposure to a temperature just sufficient to destroy its reproductive function. Heat, however, is not always applied, the preservative being sometimes relied upon for sterilization. In lieu of heat other substances have been recommended, *e.g.*, galactose.

Sometimes living attenuated bacteria are employed; again, extremely small amounts of highly virulent germs are injected, while still another class of vaccinating substances consists of bacterial products. These include bacteria split mechanically, chemically, or by autolysis, and bacterial toxins or filtrates of fluid cultures. Besredka has suggested so-called sensitized vaccines, *i.e.*, bacteria treated with their homologous specific immune sera.

Bacterial vaccines are used both to prevent and to cure infectious diseases. They are believed to accomplish this by stimulating the healthy tissues to produce substances which reinforce the normal anti-infectious powers of the body. When brought into direct contact with healthy tissues, the vaccine causes the normal cells to exercise their ability to remove foreign proteins. To accomplish this they manufacture in great abundance specific substances antagonistic to the bacteria,

called antibodies. These find their way into the circulating blood and aid the cells engaged in actual combat with the bacteria at the focus of infection. In the prophylactic use of vaccines the antibodies are stored in the blood and tissue juices ready to meet invading bacteria. The sole effect of the vaccine is the generation of antibodies and the sole action of the antibodies is upon the bacteria; therefore, it is obvious that the ultimate purpose of the vaccine will fail unless the antibodies in the blood are able to come into direct contact with the bacteria. The pathological conditions about the focus of infection are often such that accessory methods of treatment are necessary to accomplish this.

Bacterial vaccines are usually administered by subcutaneous injection, though they may be given intramuscularly or even intracutaneously; there seems to be no sufficient reason for intravenous administration, except for protein shock therapy. They have been given by the mouth and, with certain restrictions, the results have apparently been satisfactory.

**HISTORY.**—Bacterial vaccine therapy is the direct outcome of studies in immunity. Immunity is resistance to disease. Until very recently the methods practised to limit and control infectious diseases were held to be empirical, and progress seemed to be the result of accident rather than of systematic investigation; but when we thoroughly examine the history of therapeutic inoculation, we come upon illuminating facts that are not flattering to our pride in modern achievement.

While history does not reveal the precise origin and development of the methods first practised, certain isolated evidences lead us to believe that in

medicine, as in other sciences, much valuable knowledge has been lost to us. According to Pliny, Mithridates Eupator, in the first century B. C., so accustomed himself to all known poisons that none could harm him. Behring believes that knowledge of such possibilities is responsible for the Hippocratic dogma that the same factor that produces the disease is also capable of preventing it—the fundamental principle of modern homeopathy.

Descriptions by travelers of methods used by savages to protect themselves from the effects of arrow-poisons and snake-venoms are truly remarkable. Such stories suggest that these procedures are, as it were, the remnants of greater knowledge preserved among an unprogressive people. Possibly their teachers, with ever-changing modes, moved on to other scientific fashions and neglected valuable and practical facts. In this connection, Metchnikoff (*L'Immunité dans les Maladies Infectieuses*, Metchnikoff, Paris, Masson, 1901) gives the instance of Serpa-Pinto, who was immunized to snake-venom by the Vatuas, natives of the east coast of Africa. In this tribe it is the custom to extract the poison from venomous reptiles and mix it with certain herbs into a paste, which is then applied to incisions made in the skin—a painful operation followed by a swelling lasting a week. The Vatuas declare that this procedure confers a certain immunity to snake-bite. Subsequent occurrences appear to prove that Serpa-Pinto was actually immunized by this treatment. The Senegambians are said to have a method of vaccinating their cattle against bovine peripneumonia; it is certain that such a method has been known in Europe for more than a century. Inoculation against small-pox

appears to have been used in Asia for hundreds of years. The Chinese claim to have employed a method of inoculation, upon the septum of the nose, since the beginning of the eleventh century. Some writers believe that such procedures originated with the Arabian physicians, and that the practice was carried by Tartar and Chinese traders to Bengal and China.

The first publication in England describing inoculation was written by Kennedy in 1715. He stated that those who practised it asserted that it was no worse than taking the itch. The relative harmlessness claimed for inoculation did not attract serious attention until Lady Mary Wortley Montagu persuaded the profession in England to take it up. In 1721 the method was openly employed, and the success reported caused it to be used in other countries of Europe. It was brought to America during the epidemic of 1721. It is needless to say that, even though practised upon persons in good health, and the material taken from persons with only a mild attack of the disease, the inoculation was not without danger. In England the practice continued until 1840.

In certain districts of England a belief had long existed among the dairy-folk that a disease of cattle known as cow-pox, when communicated to the milkers, protected them against small-pox. It seems likely that this fact was noted particularly on account of the resistance to inoculation with small-pox of persons who had had cow-pox. Although there was apparently considerable general interest aroused by this circumstance, Edward Jenner is popularly held to have first recognized its possibilities.

[According to Alexander von Humboldt, vaccination with cow-pox had been practised by Indian shepherds of the Mexican Cordilleras "since the earliest recollection of man." Brun speaks in much the same way in reference to the Elihats of Beluchistan. The belief was general that accidental inoculation of cow-pox by the dairy-folk of England, existing prior to Jenner, in at least eighteen counties, rendered the milkers immune to small-pox.

It was a dairymaid, as is well known, who brought the fact to the notice of

his first report to the Royal Society in 1796 or early in 1797. It was rejected and in 1798 was published independently. The beneficial results of cow-pox inoculation were demonstrated almost immediately. The number of deaths from small-pox in London decreased from 17,867 and 18,477, in the last two decades of the eighteenth century, to 12,534 and 7856 in the first two decades of the nineteenth century.

SMALL-POX DEATHS.

Population.			1886	1887	1888	1889	Average of deaths.	Average per million of population.
Compulsory vaccination.	Sweden .....	4,746,465	1	5	9	2	4	1.0
	Ireland .....	4,808,728	2	14	3	0	5	1.0
	Scotland .....	4,013,029	24	17	0	6	12	3.0
	Germany .....	47,923,735	197	168	112	200	169	3.5
	England .....	28,247,151	275	505	1,026	23	458	16.0
	Switzerland .....	2,922,430	182	14	17	3	54	18.5
	Belgium .....	5,940,365	1,213	610	865	1,212	975	164.0
	Russia .....	92,822,470	16,938	25,884	*	*	21,411	231.0
	Austria .....	23,000,000	8,794	9,591	14,138	12,358	11,220	510.0
	Italy .....	29,717,982	*	16,249	18,110	13,416	15,925	536.0
Spain .....	11,864,000	*	*	14,378	8,472	11,425	963.0	

\*No statistics available.

Jenner. The first intentional inoculation was made by Benjamin Jesty, of Dorsetshire, in 1774. Small-pox was prevalent, and, though by accidental cow-pox inoculation Jesty was himself immune, he inoculated his wife and two sons near the elbow from the teats of the cows. Fifteen years later, *i.e.*, in 1789, the sons were inoculated by Mr. Trowbridge, for small-pox, together with others who had not been inoculated with cow-pox. The two Jesty boys escaped, but the unprotected went through the usual course of inoculated small-pox. Subsequent exposure to small-pox by Mrs. Jesty and the sons demonstrated their immunity. Twenty-two years after the vaccination of the Jesty family, Jenner vaccinated the Phipps boy.]

After giving this subject careful study for many years, Jenner presented

The above table from Welch and Schamberg ("Acute Contagious Diseases," Philadelphia, Lea, Publ.) shows the incidence of small-pox where vaccination is compulsory compared with its occurrence in those countries where it is not compulsory.

Nearly a century elapsed before further progress was made in artificial immunization. So long as the actual agents causing the disease remained undiscovered, empirical progress alone was possible. But with improvements in optical instruments the microscopic forms of life were discovered and the relation of micro-organisms to disease, long before suspected, was actually demonstrated. *Anthrax* was the sub-

ject of this first demonstration. In 1850 Davaine observed and described anthrax bacilli in the blood of infected animals, and in 1863, finding that they were constantly present, he suggested that they were the cause of the disease. In 1860 Delaford had cultivated them artificially in blood, and in 1876 Koch grew the anthrax bacilli on a solid medium. This work was confirmed and continued by Pasteur; both he and Koch reproduced the disease in animals.

Pasteur familiarized himself thoroughly with the prevention of small-pox by vaccination, hoping that other communicable diseases might be combated in a similar manner. Chance seems to have favored him. He had been working with his collaborators, Roux and Chamberland, upon chicken-cholera. A bacillus had been isolated the pure cultures of which could be kept alive in broth. When inoculated with these broth-cultures, healthy chickens never having had cholera, died with the typical symptoms. Identical bacilli were obtainable from the dead chickens. Upon their return from a vacation in the fall of 1879 the work was again taken up. Much to the surprise of Pasteur the broth-cultures, which had been stored away, failed to kill chickens even though the injections were in quantities much larger than in the former experiments. He immediately obtained fresh cultures from chickens which had contracted the disease spontaneously, and again demonstrated their virulence and deadly effect on normal fowls. The chickens which had been inoculated with the old cultures now proved to be entirely refractory even to large doses of highly virulent bacilli. Pasteur, whose mind

had been dwelling constantly upon the problem of the prevention of disease, immediately recognized the two facts which are the foundation of vaccine prophylaxis and vaccine therapy, namely, that *bacteria may be attenuated*, and that *attenuated bacteria may be used for vaccination*.

Believing the refractory state of the chickens to be identical with that of man after cow-pox inoculation, Pasteur called the process "vaccination." Thus, although the word "vaccine" is derived from "*vacca*," and primarily refers to the bovine species, there is sufficient justification for its retention to designate substances producing active immunity. Its use is also defensible in that it has been since 1880 the exclusive term in a literature already sufficiently burdened with newly coined words.

The work with chicken-cholera was duplicated in the case of anthrax and investigations on rabies were started.

Because of the extreme care with which every point was proved, and even after the successful immunization of dogs with attenuated spinal cord, it was five years before the first person was inoculated. Prophylactic vaccines were rapidly developed for various epizootics, such as rauschbrand, hog-erysipelas, etc. In epidemic diseases affecting man progress was necessarily slower because experimental work must proceed with greater caution. It was believed that immunity could be acquired only by recovery from a mild attack of the disease. Few were willing to submit to such a severe measure, especially when the incidence of the disease in question was not very high. It was, therefore, not until typhoid fever and bubonic plague necessitated extreme efforts and measures that Pasteur's



discoveries were extensively utilized. They would probably have remained unique instances if Wright had not elaborated methods whereby the mechanism of the changes following an inoculation could be closely observed.

By their discovery that animals could be immunized by the *products of bacteria*, Salmon and Smith opened a new field of research. Contrary to the popular belief at that time, they proved that it was not necessary to recover from an attack of a disease to become immune to it. The study of substances in the culture fluids and their relation to antagonistic properties of the blood of treated animals inaugurated work along what may be considered chemical lines instead of the previously purely biological ones. So early as 1874, Traube and Gscheidlen found that normal blood had bactericidal properties, and in 1887 Buchner, and later Nuttall, confirmed this and investigated it in detail. Discoveries of the highest importance appearing in rapid succession were the outcome of studies concerning the effect of culture fluids upon animals, and the protective power of the blood-serum of these animals. In 1888 Roux and Yersin discovered diphtheria toxin; in 1890 Behring announced the discovery of diphtheria antitoxin, and, shortly after, in collaboration with Kitasato, he prepared tetanus antitoxin. To Behring is due the credit of establishing the law that *the serum of an artificially immunized animal may transmit immunity to other animals* (passive immunity). At this point practical developments in the preparation of antitoxins ceased for a time, tetanus and diphtheria (and botulismus) being thought to be the only diseases due solely to soluble bacterial poisons. Progress continued, however,

in the development of our knowledge of the reactions on the part of the tissues following the inoculation of foreign proteins. In 1891 Ehrlich demonstrated the development of substances antagonistic to the toxic effect of abrin and ricin in the blood of animals treated by the injection of gradually increasing doses of these vegetable poisons. He studied the relations between these poisons and the antibodies in the blood-serum and learned the mechanism of *toxin neutralization*, elaborating from this the present method of standardizing diphtheria antitoxin.

In 1894 Calmette prepared serums with neutralizing properties for snake-venoms. In the same year, by injecting the washed erythrocytes of one animal into an animal of another species, Bordet produced in the second animal substances with the power of dissolving the red corpuscles of the first. These are called *hemolytic* serums. Another variety of the same class, *cytolytic* serums, have the power of dissolving or destroying tissue cells. In all cases the animal furnishing the cells and the animal injected must be of different species. *Bacteriolytic* power is one of the acquired properties of the serum of animals injected with bacteria.

According to Nicolle the work on *anaphylaxis* has shown that not only body cells and bacterial cells (*i.e.*, formed elements), when injected into an animal, undergo digestion, with the resultant formation of an excess of digestive or lytic substances, but that also unformed substances or proteins undergo the same process. In other words, the protein molecule is split into simpler substances so that it may be absorbed and eliminated. Further study has proved that several classes of sub-

stances, with different functions, are developed in the blood of animals treated with organized and unorganized protein substances. These antagonistic substances are called *antibodies* and, are the direct outcome of work along definite lines, most of it planned to demonstrate the soundness of certain theories devised to explain the occurrence of phenomena already known.

## LIST OF IMMUNIZING BODIES AND THEIR ANTIBODIES.

Antigens or immunizing substances.	Products of immunization.	
Toxins.	Antitoxins.	
Complements.	Anticomplements.	
Ferments.	Antiferments.	
Precipitogenous substances.	Precipitins.	
Agglutinogenous substances.	Agglutinins.	
Opsonigenous substances of bacteria.	Opsonins.	
Cytotoxin-producing substances.	Cytotoxins.	<div style="display: inline-block; vertical-align: middle;"> <div style="display: inline-block; vertical-align: middle;"> { Hemolysins. Bacteriolysins. Special cytotoxins. Spermatotoxin. Nephrotoxin. Hepatotoxin. Neurotoxin. Syncytiolysin, etc. } </div> <div style="display: inline-block; vertical-align: middle; margin-left: 10px;"> Consisting of two bodies, i.e., complement and amboceptor. </div> </div>

## IMMUNIZATION WITH ANTIBODIES

Precipitins.		
Agglutinins.	Antiagglutinins (?).	} antiamboceptors; the latter may be an antibody for the complementophilous or for the cytophilous haptophore of the amboceptor.
Cytotoxins.	Anticytotoxins.	
Hemolysins, etc.	Antihemolysins, etc.	

## SYNONYMS.

Complement.	Amboceptor.
Alexin.	Immunkörper.
Cytase.	Zwischenkörper.
	Intermediary body.
	Substance sensibilisatrice.
	Fixator.
	Preparator.
	Copula.
	Desmon.

(From Ricketts and Dick, "Infection, Immunity, and Serum Therapy," Chicago, Amer. Med. Assn. Press.)

the proteins used to generate them, *antigens*.

## THEORIES OF IMMUNITY.—

Few of these discoveries and developments in our knowledge of immunity have been the result of chance. They

The first of these theories—that of Pasteur—is based upon his observation that the chicken-cholera bacillus could not be grown in the filtrate from a well-developed bouillon culture of the same organism. He says: "The muscle

which has been the seat of severe disease has become, even after recovery and healing, in some manner unable to support this microbe, as if this latter, by a previous growth, had exhausted in the muscle some principle which is not restored and the absence of which inhibits the development of the organism." He believed that the mechanism of acquired immunity depended upon the exhaustion of certain elements necessary for the development of the bacterium in question.

This theory, later revived by Ehrlich under the name "athrepsia" to account for the spontaneous retrogression of certain cancers, appeared very plausible. Among those interested was Chauveau, who, although believing there was considerable experimental evidence to support Pasteur's hypothesis, thought that some observations of his own showed it to be untenable. Chauveau found that he could with impunity inoculate Algerian sheep with virulent anthrax bacilli in amounts certainly fatal for ordinary sheep, but if the dose given was very large a fatal attack of anthrax developed. He believed such results proved that immunity depended therefore not on an exhaustion of something essential to the growth of the bacteria, but upon something added to the body fluids.

The most striking point about these two hypotheses is that they both consider the body entirely passive in its resistance to infectious disease. One theory supposed that the bacteria take some property away from the body; the other, that they add some property to it.

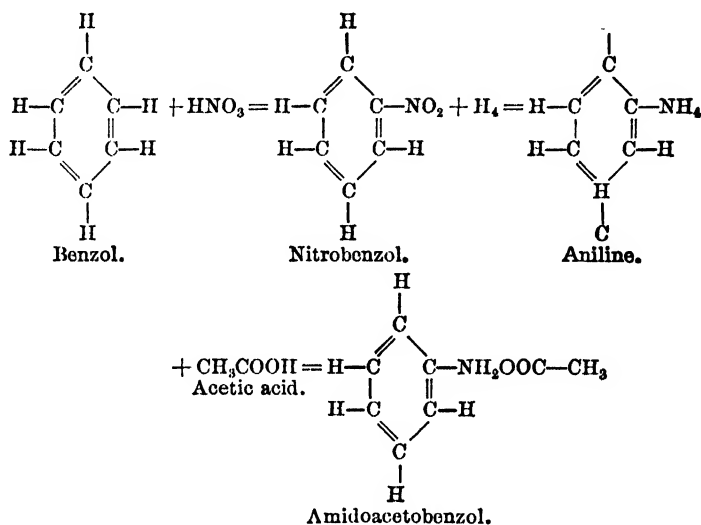
**The Phagocytic Theory of Metchnikoff.**—The activity of the white corpuscles of the blood toward foreign

particles had been noted by Virchow in 1840, and attention had been directed to their behavior toward bacteria by Koch in 1878. The first supposition that they might have some relation to immunity was made by Karl Roser in 1881. Sternberg also suggested that phagocytosis might in some way be related to immunity. Little attention was given the subject until 1884, when Metchnikoff published the results of his observations upon the activity of the leucocytes in the water-flea. The water-flea, or daphnia, is a minute aquatic animal the body of which is transparent. It is subject to a disease caused by a blastomyces. Metchnikoff observed that after the spores of this fungus had been swallowed by the animal they penetrated the intestinal wall and, entering the body cavity, were surrounded by leucocytes. The leucocytes ingested the spores and frequently caused their entire disappearance, in which case the disease was overcome. Sometimes, however, the spores were not destroyed, but developed and apparently acquired the power of killing the animal with blastomycosis.

With this observation as the starting point, Metchnikoff studied the white corpuscles of man and their relation to bacteria. He thus arrived at the promulgation of the phagocytic theory of immunity. White blood-corpuscles in the act of ingesting bacteria he called "phagocytes." The phagocytic theory of Metchnikoff supposes that immunity to infectious disease depends upon the phagocytosis of the bacteria and their destruction by a digestive process which goes on within the leucocyte. Artificial immunization increases the phagocytic power and in this way acquired immunity is established.

**The Theory of Ehrlich.**—In 1885, Ehrlich, in Germany, published a little work on the oxygen requirements of the body, in which he expressed the belief that the assimilation of foods by the body cells is accomplished by a chemical union between the food substances and some constituent of the cell. It was not his understanding that assimilation is accomplished merely by this union, because certain

fourth bond of each carbon atom is linked to an atom of hydrogen. It is well known that one or more of the atoms of hydrogen may be replaced by a great variety of radicals, and by substituting such radicals an infinite number of chemical compounds may be produced. The groups which have been substituted are called "side chains." Thus, by substituting various side chains in suc-



molecules of complex composition must be split into simpler substances before they can become a part of the protoplasm. For this reason the cell constituent which combines with the nutritious molecule serves only as a link to bring the foodstuff into relation with the digestive, oxygenizing, or fermenting activities of the cell. Ehrlich believed that his theory might be more easily understood if the center of activity of the cell were likened to the benzol ring. The molecule of benzol is  $\text{C}_6\text{H}_6$ . In the graphic representation of this formula each carbon atom is linked to two other carbon atoms in such a way that each one has three bonds of affinity satisfied. The

cession we arrive at the compound which is known commonly as acetanilid.

In exactly the same way the body cells have bonds of affinity capable of combining with various substances which are to be utilized by the cell for its nourishment.

Ehrlich further believed that the side chains of a cell consist of definite groups of atoms capable of uniting chemically with certain other definite groups of atoms in the food particles. The side chains of the cells are called *receptors*, while the combining groups of atoms of the food substances Ehrlich called *haptophore groups*. Now, as we know, different foods have different chemical

compositions, and Ehrlich believed it likely that the binding groups or receptors of the cells are also different in chemical composition and affinity to agree with the peculiar affinities of the food materials. In other words, it is a fundamental requirement of this theory that there must be as many different kinds of receptors as there are substances capable of uniting with the cell.

In order to explain the formation of antibodies by the side-chain theory of nutrition Ehrlich supposes that all protein materials, not only those used for the nourishment of the cells, but also toxins and other substances harmful to the cell, unite with the receptors in the same way. Instead, however, of the receptor acting merely as a link between the food material and the cell, in the case of noxious substances, an effort is made to protect the cell by eliminating the affected receptor. When the receptor has been eliminated a wound or defect is left upon the cell. This wound is healed by the production of new receptors, and, as occurs in all reparative processes, an excess of material is manufactured. But as only one receptor is necessary to replace it all others are thrown off into the body fluids. Blood-serum rich in such receptors constitutes the immune serum resulting from the treatment of an animal with specific proteins. In other words, the free receptors in the blood-serum are the immune bodies.

The cells of the body may possess no receptors for certain protein substances, and when this is the case the animal is naturally immune to these substances; for example, the human body has no receptors for the substances which cause hog-cholera.

There are assumed to be, then, as

many different receptors as there are substances which can unite with the cell. There are likewise several classes of receptors with regard to their relation to and effect upon the antigen. By *antigen* we understand the substance used to stimulate the production of receptors, or, as they are collectively called, antibodies. After these have been set free by the cell they become a constituent of the serum and may be handled as such. They may be recognized and their quantity estimated by test-tube experiments just as if they were chemical substances. To Behring we owe the discovery that in the blood-serum, or a derivative of it, antibodies may be transferred to another animal with specific effect either in the treatment or in the prevention of the disease in question.

The theories of Metchnikoff and Ehrlich seeking to explain the various phenomena of resistance to and recovery from infectious disease, while possessing little in common, are not essentially contradictory. Each theory is based upon the ordinary processes of the body, that is to say, those concerned directly with the nutrition of the body cells. Metchnikoff held at first that the leucocytes, and they alone, were the agents responsible for meeting in combat the bacteria invading the body tissues, and that the issue of this combat is either immunity or an infection which may result in recovery, chronicity, or death.

Ehrlich and his school worked along chemical lines, and while recognizing the phenomenon of phagocytosis did not attach great importance to it. According to this school, acquired immunity is the result of phenomena which may be explained upon chemical

grounds, and that practically all the changes taking place in the tissues may be demonstrated in the test-tube. With the serum of an immune animal, for instance, toxins may be neutralized and bacteria killed and digested. As first shown by Bordet, two substances are necessary to accomplish the destruction of micro-organisms; one is the newly formed substance appearing in the blood-serum as a result of immunization; the other (called complement, because it completes the action of the first) is present in any fresh serum whether the animal has been immunized or not. The complement is thermolabile, that is, a moderate degree of heat will destroy it, and it cannot be preserved for more than a very few days.

**The Theory of Metchnikoff.**—Metchnikoff holds that the complement is derived from the leucocytes and also that it is not set free until the leucocytes are destroyed. Briefly, there is no free complement in the circulating blood under ordinary circumstances.

This was Metchnikoff's most important point after the school of Ehrlich had demonstrated that practically all the reactions of immunity could take place outside the body without the leucocytes. This final point was shown by Wright to be the neutral ground between the two theories of Ehrlich and Metchnikoff. Wright demonstrated that leucocytes are necessary to the body in overcoming or resisting the effects of bacteria, while the body fluids are equally important in that they prepare the bacteria for final ingestion and digestion. When it was demonstrated that there is more phagocytosis in a mixture of leucocytes, immune serum, and streptococci, than in a mixture of normal serum, leucocytes, and strepto-

cocci, Metchnikoff believed that this proved the presence in the serum of a substance stimulating the leucocytes to greater activity. He called this substance *stimulin*.

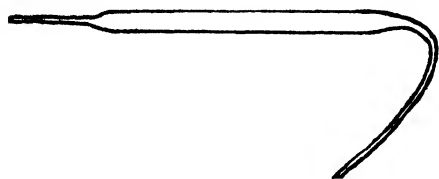
Denys and Leclef were the first to question the exact function of the so-called stimulin. Their work led them to believe that the immune body in the serum of a treated animal does not essentially affect the leucocytes, but that its chief effect is upon the bacteria, changing them in some way so that they are more easily ingested by the leucocytes.

Having in mind the observation of Metchnikoff and others with regard to increased phagocytosis in a mixture containing immune serum, Leishman attempted to determine whether he could estimate the degree of immunity of a vaccinated person by observing the relative amount of phagocytosis in mixtures containing normal serum compared with one containing serum from immunized persons. For this purpose Leishman measured in a capillary tube equal volumes of a bacterial suspension of appropriate density and blood drawn from the finger. These were mixed on a slide, covered with a cover-glass, and incubated at body temperature for fifteen minutes. The slide and cover-glass were then drawn apart by a sliding movement, and the films thus obtained stained by Leishman's modification of Romanowski's stain and examined under the microscope. The average number of bacteria per polymorphonuclear leucocyte was thus estimated by Leishman, and he compared it with a similar average calculated from specimens prepared with normal blood.

By this technique Leishman was able

to show a certain relation between the degree of immunity of an inoculated person and the degree of phagocytosis. But since he did not take into consideration the work of Denys and Leclef, and believed that he was working with immune bodies which stimulated the leucocytes, his conclusions lost much of their significance.

Wright and Douglas modified this technique by using capillary tubes instead of a slide and cover-glass for the incubation, afterward making film preparations in the ordinary way. Furthermore, the coagulation of the blood was prevented by the use of sodium citrate, thus avoiding com-



Wright capsule.

plications dependent upon coagulation, and making it possible to separate the white corpuscles from the blood-plasma by centrifugalizing, decanting, and washing. The first method elaborated by Wright and Douglas was further refined and modified to the "opsonic-index technique."

**The Opsonic Index.**—The object in this procedure is to compare the average number of bacteria ingested by healthy leucocytes when incubated respectively with serums from healthy and from infected individuals.

Neufeld and Rimpau, working independently of Wright, described substances in the blood-serum of animals immunized to the streptococcus and pneumococcus which they called *bacteriotropins*.

Again, Simon, Lamar, and Bispham,

in examining their slides, do not estimate the number of bacteria found in the leucocytes, but rather the percentage of leucocytes which actually take part in the phagocytic process, that is to say, those which contain bacteria. By the method of dilution they determine what they have called the "opsonic coefficient of extinction." The general opinion of other workers appears to be that the results obtained by this modification are practically identical with the results obtained by the original method of Wright.

Wright, with coworkers and students, undertook a systematic study of the relation of blood-serum to phagocytosis. He determined the direct dependence of phagocytosis upon certain substances contained in the blood-serum. He proved conclusively that this serum component acts upon the bacteria directly, not upon the leucocytes, and that it is bound by the bacteria and renders them subject to phagocytosis. This fact of preparing or modifying the bacteria in such a manner that they are rendered easy prey to the phagocytes Wright called an opsonic effect (*opsono*, I cater for; I prepare victuals for), and he employed the term "opsonins" to designate the substances in the blood-fluids which produce this effect.

**Nature of Opsonins.**—Opsonins are of two kinds: normal opsonins, those which are thermolabile (those destroyed by heating to a temperature of 55° C.), and immune opsonins, those which are thermostabile. It has been suggested that normal opsonins are in reality identical with complement, while immune opsonins are identical with amboceptors (Neufeld and Hüne; Levaditi and Inmann). This view was based not only on the

thermolability of normal opsonins, but also upon the fact that opsonins may be removed from normal serum with the complement by the method of complement fixation. Wright contends that the opsonins have a distinct identity. The observations of Dean and Hektoen appear to support this contention, but the matter is not definitely decided.

The *specificity* of opsonins and their *multiplicity* have been shown by Hektoen and Ruediger.

It has been demonstrated, indeed, that the opsonic substances may be absorbed from serums by treating them with various species of bacteria, just as specific agglutinins may be absorbed out of an agglutinating serum by the method of absorption. Cold seems to have no influence upon the opsonic power of a serum, but its activity is gradually lost when it is exposed to sunlight.

**Source of Opsonins.**—As already stated, Metchnikoff believed the leucocytes to be the source of all bacteriotropic substances, while Ehrlich held that any cell affected by the antigen was capable of being stimulated to produce immune bodies.

Wright believes that opsonins are produced locally at the site of inoculation, and in favor of this cites the fact that when toxins are injected subcutaneously in horses there is a greater production of antitoxin than when the toxin is injected intravenously. Again, patients who show a considerable local reaction at the site of inoculation are apparently immunized more effectively than those who suffer with constitutional symptoms but without appreciable local reaction. Also, local immunity may be acquired and retained apart from the acquisi-

tion or retention of general immunity. A local form of immunity illustrating this point is the sensitized conjunctiva. If a weak solution of precipitated tuberculin is dropped into the eye of a normal individual no reaction follows. If after a certain number of days, however, tuberculin is again dropped into this eye there occurs the same kind of a local reaction as if the person were tuberculous. The other eye, on the contrary, shows no change at all.

Sajous, in 1907 ("Internal Secretions," vol. ii, p. 1093), advanced the view that the thyroid and parathyroid glands, which show marked activity during infections, were the original source of the opsonins, owing to the sensitizing action of their secretion upon all bodies, including bacteria, which contain phosphorus. This view has been sustained by the experiments of Marbé (C.-r. de la Soc. de Biol., vol. lxiv, 1908), of the Pasteur Institute, who found that while removal of the thyroid caused a considerable decline of opsonic activity of the blood-serum, the administration of thyroid gland increased it markedly; and also by those of Stanoff (C.-r. de la Soc. de Biol., vol. lxvi, p. 296, 1909), likewise in the Pasteur Institute, which led him to ascribe "the opsonizing action of thyroid extract to the thyroglobulin of Oswald, which is normally present in the thyroid gland." Sajous's theory harmonizes with all others in the sense that it aims only to show whence the opsonins found in the body cells are originally derived.

**Practical Value of Opsonic-Index Determinations.**—The question of the utility, value, and necessity of opsonic-index technique was much discussed a



few years ago. This discussion concerned first the accuracy of the method and then the necessity for it. It seems certain that in the hands of a careful, trained technician the method is sufficiently accurate to indicate the relative content of the blood in certain bacteriotropic substances. To prove this a long series of estimations of the opsonic indices have been made. In normal individuals the tuberculo-opsonic index estimations were found to vary from 1.2 to 0.8, the majority of individuals being practically equal, 1.0. This variation is considered normal. "Wild" counts are said to occur occasionally, but as a diagnosis and plan of treatment are not based on a single estimation this objection loses much of its force. Since there are other antibodies in the blood besides opsonins, the question has been raised whether the index may not give a wrong idea of the patient's resistance to certain bacteria. May not the opsonins be low when certain other antibodies are relatively abundant? In answer to this Wright has said that, although there are other antibodies, opsonins are by far the most important. This dictum has apparently not been universally accepted. It cannot be denied that in general the opsonic index follows closely the clinical improvement and increase in the severity of the infection. Wright has consistently maintained that to treat an infection intelligently one must study the course of events following the inoculations of the vaccine by determinations of the opsonic index, and that clinical observations cannot give evidence of sufficient value to constitute a guide for therapeutic inoculation. The whole system of bacterial therapeutics as practised today has been built upon studies

of the opsonic index in connection with inoculations made by Wright and his pupils, and accepted as the guide by them with regard to dosage, intervals between doses, and accessory methods of treatment.

A far more weighty and practically insurmountable objection to the opsonic-index estimations is the time required. In spite of the many good arguments adduced to support his contentions, utilitarianism, if nothing else, has decided upon the negative side. In textbooks published in England and in English medical journals one still reads reports of cases the treatment of which was controlled by opsonic-index determinations, but such reports are rare from any other source. By common agreement in this and other countries it has been decided that clinical control of dosage, of intervals between doses, and of accessory methods of treatment, is sufficiently accurate and reliable for the satisfactory treatment of the great majority of cases. For the general practitioner the necessary laboratory work is too difficult and too time-consuming, and the cost of consultation with a trained bacteriologist would be so great as to restrict vaccine therapy to a very small class of patients.

The technique recommended by Wright and believed by him to be necessary to careful work has therefore been relegated to medical history, while the practical application of bacterial vaccines to the treatment and prevention of disease has gone forward by leaps and bounds. The opsonic index has, however, left footprints in the form of words, to understand the exact meaning of which we must be familiar with the train of events following the inoculation of a vaccine.

**BACTERIAL VACCINES.—***Changes which Follow Inoculation.—*

The changes in the bacteriotropic power of the blood which follow the inoculation of a bacterial vaccine were for the first time tested quantitatively upon man in connection with Wright's results in antityphoid vaccination. The work on typhoid was followed by still further researches with regard to the vaccine treatment of Malta fever, tuberculosis, bubonic plague, pneumonia, staphylococcus and streptococcus infections, etc. In all of these the same train of events occurs. After the injection of the vaccine there is a period of diminished resistance which is characterized by a decline in the antibacterial power of the blood. This decline is called the *negative phase*, and it is accentuated and prolonged in proportion to the size of the dose of vaccine injected. If a large dose of vaccine has been used the negative phase may be characterized, clinically, by a rise in temperature and by other constitutional disturbances. If a small dose has been given, the negative phase may be entirely unaccompanied by clinical symptoms. The negative phase is followed by a *positive phase*. Its characteristic is an increase in the antibacterial power of the blood, corresponding to a period of increased resistance. The curve graphically representing the estimation of opsonic indices after inoculation describes a downward course corresponding to a negative phase, then rises gradually to a sharp peak constituting the positive phase, after which it sinks first comparatively slowly and then more rapidly. During the positive phase there is usually a sense of increased physical vigor and improvement in the general symptoms. After the negative

and positive phases of which Wright has spoken as "the ebb and flow and reflow of the tide of immunity," the blood may be maintained for a variable period at a somewhat higher level of antibacterial power than before inoculation, or, as in some chronic and otherwise resistant infections such as tuberculosis, it may go down more rapidly, and in the course of ten days reach the point at which it was before the inoculation.

In the treatment of animals for the production of antitoxins, it is possible by repeated and gradually increasing injections to raise the antitoxic power of the blood to a very high point. At first, it was naturally believed that something of the kind would be possible with the administration of bacterial vaccines; but such an *accumulative effect* in the direction of the positive phase has been found impossible. On the contrary, the opposite condition may arise and must be reckoned with; that is, if repeated excessive doses of a vaccine are given, instead of a slight negative phase appearing after each, the negative phase may be forced down until the patient is in a very serious condition, or death supervenes.

Upon such observations Wright was able to formulate a system of dosage which more than any other single factor was responsible for placing bacterial vaccine therapy upon a practical basis. He was able to show that extremely small doses of killed bacteria were sufficient to elicit an immunizing response of therapeutic value. By means of the opsonic-index method he determined the dosage of bacteria necessary to evoke such an immunizing response. It is true that at the present time we have discarded the opsonic

index as a guide to dosage, but it must be remembered that we have the experience of many years to guide us. We know now that, except in tuberculosis and possibly certain other infections in which the patient is very weak and toxic, bacterial vaccines are practically harmless. The greatest harm that may follow too large a dose is a severe local reaction resulting in temporary discomfort to the patient.

The *optimum dose* of a bacterial vaccine causes a transient negative phase which, clinically, is scarcely or not at all recognizable, followed by a positive phase coincident with improvement in the symptoms.

*Classification of Bacterial Vaccines.*

—The vaccine is called *autogenous* when it is made with cultures obtained from the patient's own lesions. *Stock* vaccines are those made of representative types of the organisms in question. In order that stock vaccines may be of the greatest value and have the widest range of efficiency they are generally *polyvalent*, that is, they contain a large number of different strains of the same bacterial species, or the same strain from different sources. Polyvalent vaccines are to be distinguished from *mixed* vaccines, the latter being those containing two or more strains of different species and intended for treatment in mixed infection.

Although it is generally true that autogenous vaccines are of greater value than stock vaccines they cannot, in general practice, be used universally. Furthermore, if an accurate diagnosis has been made, it is only in a relatively small percentage of cases that the autogenous vaccine is necessary. The first consideration that makes stock vaccines a necessity is the cost of the autogenous

product. Only in institutions with well-equipped laboratories can special vaccines be made for each case. In private practice, except in obstinate cases or those of unusual and mixed infections, the expense compels the use of stock vaccines almost entirely. Because of the great variety of their types there are some bacterial species which nearly always necessitate the employment of an autogenous vaccine. This is particularly true of streptococcic and *B. coli* infections. Besides the expense involved there is the consideration of time. In very acute diseases, such as pneumonia and puerperal septicemia, on account of the time required to prepare the autogenous vaccine, the use of a stock vaccine, for the earlier doses at least, is imperative.

Attempts have been made to prepare autogenous tuberculins by an antiformin method, but at the present time the work is too laborious to be of practical value. In this method, the sputum, secretion, or the material containing the organisms is shaken up with antiformin and allowed to stand in the incubator, or at room temperature, for several hours. The antiformin dissolves all bacteria except the acid-fast bacilli. The material is then placed in the centrifuge to throw down the tubercle bacilli. The supernatant fluid is decanted and the sediment is carefully washed two or three times with sterile normal saline solution, after which the tubercle bacilli are spread upon the surface of some suitable medium, such as Dorset's egg-medium, and incubated. A visible growth may be obtained in this way within a few weeks. This growth may be collected and made into a tuberculin. On account of their waxy envelope the tubercle bacilli should

never be used whole, but only after dissolving the wax chemically, or carefully and thoroughly grinding the bacilli in a ball mill.

Gonorrheal rheumatism may be treated with stock vaccines only, unless, indeed, there is a coexistent urethritis. The work of Hamilton seems to show that there is no advantage in using an autogenous gonococcus vaccine. Gonorrheal rheumatism is an example of several conditions which, on account of the difficulty or impossibility of obtaining the infecting organism from the focus of infection, must be treated with stock vaccines. In conditions like chronic posterior urethritis, it is advisable to add to the autogenous mixed vaccine the stock gonococcus culture, even though the gonococcus may not be demonstrable culturally. It is very difficult to isolate the gonococcus at this stage, and it is therefore safer, even though not demonstrable, to consider it present.

**DIAGNOSIS.**—The diagnosis may be made in four ways: first, by clinical observation and deduction; second, by stained smears; third, by cultural methods; and fourth, by serological reactions. For the general practitioner the first will certainly be the most popular, and in many cases may be considered entirely safe. For instance, the common cause of suppuration in superficial wounds and ordinary furuncles is nearly always the staphylococcus. The predominant organism in yellow pus we conclude to be the *Staphylococcus aureus*, in green pus the *Bacillus pyocyaneus*, etc. Wright has pointed out that in infections above the diaphragm, connected either directly or indirectly with the respiratory passages, the pneumococcus is one of the most frequent

offenders, while below the diaphragm the colon bacillus plays the same rôle.

Diagnosis by the examination of stained smears is the routine procedure in tuberculosis and gonorrhea. The microscope is frequently of assistance in demonstrating the type of pneumonia, of cerebrospinal meningitis, and of a host of other conditions. Up to the present time clinicians have given little thought to organisms other than those reputed to be the causative agent in the condition under examination. Little or no attention is regularly paid to streptococci and staphylococci in the routine examination of sputum for tubercle bacilli. If acid-fast rods are seen the diagnosis is dismissed as positive. Diagnosis by the examination of stained smears is entirely inadequate for mixed infections of all kinds. The vaccine therapist must know all the types of bacteria present in the lesion. Indeed, in not a few mixed infections, after the lapse of two or three weeks, the initial etiological factor has become the least important of the bacteria present. Many failures in the vaccine treatment of such diseases as typhoid fever, influenza, and whooping-cough are undoubtedly due to the fact that this is not recognized. The isolation of the bacteria requires a well-equipped bacteriological laboratory with proper facilities for making the various culture media. The region of the body in which the lesion is located and the type of infection largely determine the particular technique and the culture media to be chosen for the isolation and study of the bacteria; for instance, the isolation of the acne bacillus requires methods very different from those used for the gonococcus.

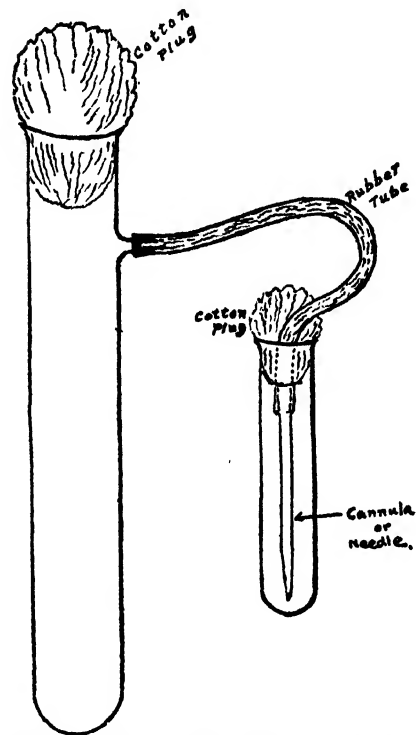
*Blood-cultures.*—In blood-cultures

we have a direct and positive method for making a diagnosis; and if the proper technique has been employed, the cultures obtained are pure, and may be used immediately for the preparation of autogenous vaccines.

During the first week of the disease, blood-cultures offer the easiest method for the isolation of the typhoid bacillus. Later, the bacillus disappears from the circulation, and its isolation then, from the feces, is attended with greater difficulty. A high percentage of cases of pneumonia yield, in the early stages, pure cultures of the pneumococcus. In other bacteremias, also in septicemias, and in pyemia, representative organisms are readily obtained by blood-cultures.

The blood is preferably withdrawn from one of the veins at the bend of the elbow, or from the internal saphenous vein as it passes upward in front of the internal malleolus. The skin should be carefully cleansed, first with soap, then with alcohol and ether, and finally painted with tincture of iodine, or 5 per cent. iodine in acetone. If iodine is used the specimen may be taken almost immediately, whereas with bichloride or some of the other antiseptics it is better to wait an hour before beginning the operation. The syringe must be of some sterilizable variety, and, while it may usually be sterilized by boiling for twenty minutes, it is much safer to sterilize it in the autoclave. If the syringe should happen to be contaminated by a spore-bearing organism, boiling, even for an hour, may not destroy the spores. Before placing it in the autoclave the syringe may be put into a test-tube with cotton in the bottom to protect the needle, or it may be wrapped in paper or gauze. If the syringe is of the "all glass"

variety, or if it is a "Record"—which is probably the best for the purpose—it is advisable to sterilize the barrel and plunger separately. Otherwise difference in expansion may cause the barrel to break. When everything is in readiness a tourniquet of soft rubber tubing is wound tightly around the



Cannula and side-neck test-tube as used by Noguchi for the collection of blood.

upper arm at about its middle third. This makes the vein stand out prominently and the syringe needle may be inserted easily. It should be pointed toward the shoulder. Great care must be taken to avoid the entrance of air into the vein. In very stout individuals it is sometimes necessary to dissect out the vein. Instead of a syringe one may use an ordinary syringe needle attached

## PLATE I,

Fig. 1.

**Blood-cultures.**—Withdrawing blood from vein at bend of elbow. One flask contains a large amount of bouillon, one a small amount, and one bouillon with chalk.

Fig. 2.

**Washing Sputum.**—Right. With sterile forceps, a little mass of the sputum is shaken successively in six flasks containing sterile saline solution.

**Inoculating Blood-agar Plate with Glass Rod.**—Left. For the isolation of the bacteria, the washed sputum (or a tiny drop of culture pus, urine, or other infectious material) is placed upon the surface of the blood-agar and smeared carefully over the whole surface with a sterile glass rod.

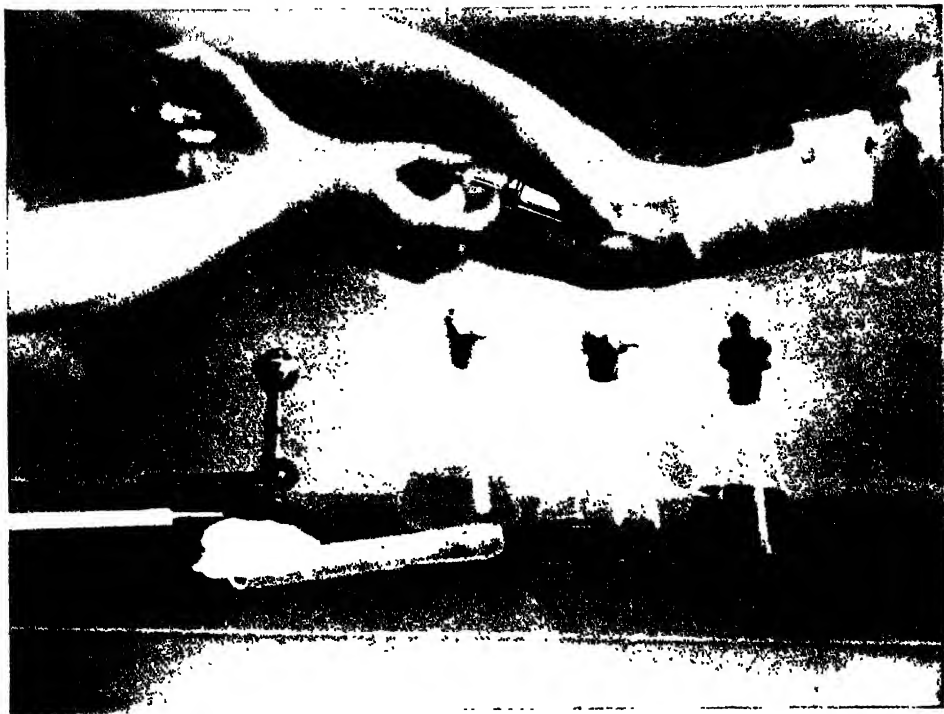
# PLATE I

**Blood-cultures.**—With a sterile pipette draw blood from vein in back of elbow. One flask contains a large amount of blood and one a small amount and one position with sterile flask.

## Fig. 2.

**Washing Sputum.**—Right With sterile forceps a little amount of the sputum is shaken successively in six flasks containing sterile saline solution.

**Inoculating Blood agar Plate with Glass Rod.**—Take the the isolation of the bacteria in the washed sputum for a day. of culture and urine or other infectious material is placed upon the surface of the medium and smeared evenly over the whole surface with a sterile glass rod.







to a rubber tube, leading either directly or by an attached glass tube into a sterile flask. If a syringe is used the blood must be immediately forced out into a sterile flask or into the culture medium. It is preferable to make the culture directly at the bedside, but the blood may be drawn into flasks or test-tubes containing a sterile solution of sodium citrate (1.5 per cent.) or ammonium oxalate (0.2 per cent.) to prevent coagulation. The advantage is that a much greater length of time may be allowed between the withdrawal of the blood and the making of cultures, thus allowing time to transmit the specimen to the laboratory, possibly overnight.

Three flasks of dextrose bouillon should be inoculated with varying quantities of the blood. One of the flasks should contain a very small quantity, so that any antibodies present may be so diluted that they will not inhibit the growth of the bacteria. On account of the high acid production of streptococci and pneumococci, Hiss has recommended the addition of one gram of powdered calcium carbonate to one of the flasks in order to neutralize the acid and permit these cocci to develop.

The best medium for cultures from typhoid patients is a so-called enriching medium composed of ox-bile containing 10 per cent. of glycerin. When this is not available ordinary bouillon seems to give good results. Russell and others have been successful in isolating the typhoid bacillus from specimens of blood obtained from the lobe of the ear. The skin is cleansed in the ordinary way and the blood is received as directly as possible into a sterile Wright capsule. The coagulation of the blood seems to offer no hindrance to the development

of the typhoid bacilli as it does to more delicate organisms. Another great advantage of this method is that the specimen may be sent long distances to the laboratory. Staphylococci and diphtheroid organisms in blood-cultures should be regarded with considerable suspicion, since they often occur as skin contaminations. This is especially true of *Staphylococcus albus*, but even when a *Staphylococcus aureus* is obtained a corroborative culture should be made. If after twenty-four hours an uncontaminated growth is found in the bouillon culture, the autogenous vaccine may be made directly from it without further manipulation. But the evidence that the culture is pure must be unquestionable.

#### *Collection of Infectious Material.*—

For the collection of infectious material from various parts of the body for diagnosis and for the isolation of the various bacteria present in the lesion, expensive and unusual apparatus is entirely unnecessary.

Because of the possible differences in rapidity of growth and other biological characteristics of the bacteria, it is advisable to submit to the laboratory for examination a smear upon a microscope slide, a culture made directly from the patient, and a specimen of the infectious material in a sterile tube. It is sometimes best to send infectious material dried on a sterile cotton swab. As a rule, the bacteria remain alive in the dried state, and there is no danger that the more vigorous will overgrow the more delicate.

*The Slide.*—Microscopic examination of a stained smear is always advisable. The slide is allowed to dry in the air, then fixed by heating gently over the free flame until when held flat, back

down, against the hand, it feels hot, but does not burn. It is then allowed to cool, stained, and examined or wrapped in clean paper and sent to the laboratory.

*The Swab.*—The swab should be handled so carefully that it does not touch anything except the material from which the specimen is to be obtained. It is removed from its tube, brought in contact with the infected area, smeared upon the surface of the culture medium, and returned to its tube.

*The Bulb Pipette.*—Some of the infectious material is then drawn into the bulb pipette. This is accomplished by aspiration, the end of the pipette being, of course, plugged with cotton. If the pipette is small a rubber tube such as is furnished with the Thoma-Zeiss blood-counting pipettes may be attached to it. Both ends of the bulb should finally be sealed, care being taken that the material in the bulb is not overheated. No antiseptic should be used locally for several hours previous to the collection of the infectious material.

These directions are intended for those who do not live conveniently near a well-equipped laboratory, and at the present time fully one-half the practitioners in America seem to be so situated. If the material can be delivered at the laboratory within a few hours the infectious material may be collected on a swab, in a pipette, or in a sterile bottle or other receptacle. If the specimen is collected by a bacteriologist it is likely that he will transfer the material directly to suitable culture materials. In collecting the material, it should be borne in mind that the purpose is to obtain exactly the material concerned with

the infection, excluding all extraneous bacteria. It is to be remembered that every object with which the instruments come in contact is contaminated with just such extraneous organisms; if they gain access to the specimen, they may outgrow and obscure the bacteria causing the disease. It is therefore important to protect the point from which the specimen is to be taken, and to remove beforehand, as thoroughly as possible, everything that might harbor bacteria.

In obtaining material from the external meatus of the ear and from the nose, a sterilized speculum of the Gruber pattern, or one of its modifications, should be used. When sputum is collected, the specimen should be the first that is coughed up in the morning. It should be taken after the patient has thoroughly scrubbed his teeth and has gargled his throat with sterile salt solution. Dr. Martha Wollstein has been successful in collecting bronchial secretions from children by using a mouth-gag and touching the pharynx with a cotton swab. This causes the child to retch, when the material is brought forward and projected against the swab. One should never attempt to collect material from the mouth or pharynx without the use of a tongue-depressor. When the specimen is to be collected from the conjunctiva there should be no preliminary cleansing, as this might wash away the few bacteria present. To collect pus from the male urethra cleanse the glans and insert the end of the pipette into the meatus; if no pus appears the urethra may be stripped forward. The female urethra is easily stripped by inserting the index finger into the vagina; press on the upper wall and gently bring the finger forward

while the labia are held apart. The uterus should be pulled down with a tenaculum when a specimen is to be collected from the cervix or a sterile cylindrical speculum is inserted into the vagina. Never allow the swab to touch the sides of the speculum or to enter the uterine cavity. The danger of carrying infection into it is so great that no risk may be taken. Soiling the outside of the tube or container with infectious material is especially to be guarded against; the infection may be due to an extremely virulent organism of a particularly dangerous or epidemic disease. Should there be any suspicion that the tube has been thus soiled it should immediately be flamed or burned, boiled, or soaked in a strong antiseptic.

*Culture Media.*—The best general culture medium for the isolation of pathogenic bacteria is blood-agar. If there are no other facilities at hand for obtaining blood, a small amount, sufficient for several tubes or plates of agar, is easily obtained by pricking the finger. After winding a bandage around it, it is carefully cleansed and pricked just back of the nail with a sterile needle or sharp glass point. The blood is collected directly in a capillary pipette and then transferred to the culture medium, or it is allowed to drop directly into the tube. If this is done with ordinary care there is little danger of contamination. Small quantities of blood may be obtained from the ear-veins of a rabbit and used in the same way. For larger quantities it is convenient to bleed an anesthetized rabbit or guinea-pig directly from the heart, 5 to 10 c.c. of blood being easily obtained with a sterile syringe and needle and being at once transferred

to a flask containing glass beads. The flask is shaken until the fibrin has formed, the beads defibrinating the blood. The results are generally very satisfactory. Human corpuscles are usually considered preferable, but the corpuscles of the horse, sheep, goat, calf, or rabbit are a satisfactory substitute.

For isolating organisms upon blood-agar it is best to use Petri dishes, those with porous tops being generally preferable. About a cubic centimeter of defibrinated blood is added to a tube of melted agar which has been cooled to between 40° and 45° C. After thorough mixing this is poured into the Petri dishes. Since the blood-agar plates should always be incubated twenty-four hours before they are used, it is advisable to have a stock always on hand. They may be preserved in the refrigerator for some time without deterioration. For inoculating these plates, a drop of the infectious material is placed on the surface of the culture medium and is smeared well over the entire surface with a sterile glass rod. This same rod is then smeared over the surface of a second, third, and sometimes a fourth plate. This procedure serves to so dilute and spread the bacteria in the infectious material that after twenty-four hours' incubation single colonies may be easily fished from the third or fourth plate.

Instead of plating the material directly it is sometimes advisable to shake a small quantity in a tube of bouillon or sterile salt solution and transfer a drop of this fluid to the surface of the Petri dish, especially if the material has been dried. In this case, it is also sometimes of advantage to incubate the tube of bouillon

for a few hours before making the smears upon the plates.

Allen (*Journal of Vaccine Therapy*, vol. i, No. 1, January, 1912) gave the following directions for the *isolation of the acne bacillus*: "For the cultural examination the following materials are necessary: Two plates of agar-agar, two plates of medium of the following composition: Agar-agar 3 per cent., to which has been added while fluid an equal part of a mixture of pure oleic acid and ascitic fluid or of ox-blood serum, and sufficient saturated solution of neutral red to tint the whole a bright red, the whole being thoroughly mixed before being poured into the Petri dish; also four or five tubes of peptone broth, and a suitable apparatus for anaërobic incubation. Personally I find a glass cylinder eight inches high and four inches in diameter all that is needed. A mixture of saturated aqueous solutions of caustic soda and pyrogalllic acid is poured into the cylinder for a depth of two or three inches, the culture tubes placed inside, and air excluded by means of a good cork, over which melted paraffin is poured. Sebum from non-pustular and secretion from pustular foci are distributed over the various plates and mixed with the peptone broth. All the plates and one or two of the tubes are incubated aërobically at 37° C. for twenty-four to thirty-six hours, while the remainder of the tubes are subjected to anaërobic culture in the above apparatus. Sometimes both the *acne bacillus* and the *staphylococcus* can be secured with ease in pure culture from the plates; should colonies of the former, however, fail to appear, then the anaërobic incubation of the tubes should be continued for

about a fortnight. After this interval most of the *staphylococci* will have died, whereas the *acne bacilli* will have multiplied. By inseminating a loopful or two of the well-mixed broth upon a plate of the oleic acid-serum-neutral red medium and incubating aërobically for twenty-four hours discrete colonies of the *acne bacillus* will be readily obtained and be available for planting upon slopes or plates of the above medium. Should *staphylococci* have been present in the various foci, no difficulty whatever will be experienced in their isolation from the agar plates after twenty-four hours' aërobic incubation."

For the *isolation of the gonococcus* the medium of choice is a neutral agar containing ascitic or hydrocele fluid. Human blood-serum is valuable, but more difficult to obtain. The medium is greatly improved by adding 5 per cent. glycerin or 1 per cent. dextrose. The *gonococcus* is extremely delicate and its isolation cannot be successfully accomplished if the pus is allowed to become chilled. The smears on the plates must therefore be made as quickly as possible and the plates placed in the incubator.

Plates inoculated in this manner are removed from the incubator and isolations made after twenty-four hours (colonies fished should be marked with a blue pencil upon the bottom of the plate), after which they may be reincubated for another examination at the end of forty-eight hours. The colonies present are studied with an achromatic triplet lens, or, better, with a binocular microscope. Several of each type found are transferred by means of a sterile platinum wire to suitable media in tubes. A tube containing a solid

## PLATE II.

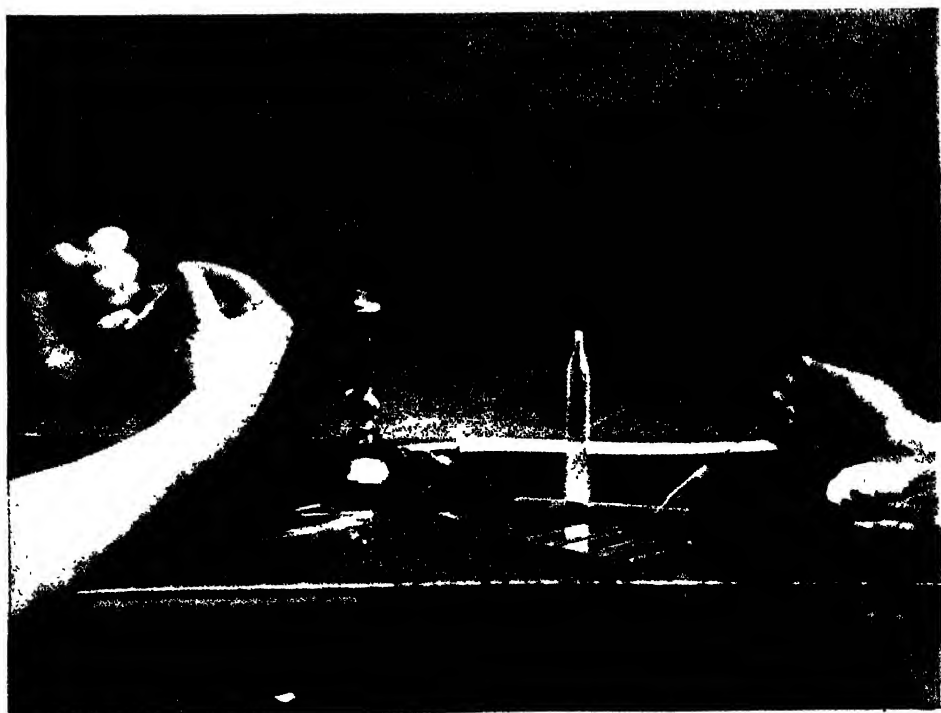
Fig. 1.

**Collecting Isolated Colonies from Blood-agar Plate with sterilized platinum wire.**

**Collecting Specimen of Blood in Wright Capsule.—Left. Mixing Equal Parts of Blood from Finger and Bacterial Suspension in Capillary Pipette.—Right. The sealed tube standing upright upon a block of "plasticine" contains the thick suspension of bacteria. After counting, this will be diluted with saline solution. The small tube standing slanted in the plasticine contains a sample of the thick suspension, removed for counting. The pipette contains a column of blood, and an equal quantity of the thick suspension is being taken up.**

Fig. 1.  
Collecting Isolated Colonies from Blood-agar Plate with  
sterilized platinum wire.

Collecting Specimen of Blood in Wright Capillary - 1.0  
Mixing Equal Parts of Blood from Finger and Bacterial  
Suspension in Capillary Pipette - Right. The sealed end  
standing upright upon a block of "paraffine" contains the  
specimen of bacteria. After counting this will be placed in  
sterile solution. The small tube standing slanted in the glass  
tube contains a sample of the thick suspension, removed for  
counting. The pipette contains a column of blood, and an equal  
quantity of the thick suspension is being taken up.







medium and a tube of bouillon should be planted from each colony. Here again blood-agar is the best solid medium for general use.

The following medium has been suggested by P. S. Pelouze and L. E. Viteri: A calf's brain (weighing approximately 500 Gm.) is forced through wide meshed gauze into 500 c.c. of distilled water and placed in the ice box for 24 hours. It is then filtered several times through cotton of varying degrees of compactness. The resultant fluid is turbid no matter how often it is filtered. To this filtrate is added 0.5 per cent. acid sodium phosphate and 1 per cent. peptone. It can now be autoclaved at 15 pounds pressure for 20 minutes and kept as stock, or the final steps for its completion can be carried out. To complete the medium it is simply necessary to add 1 part of the brain bouillon to 3 parts of standard 2.5 per cent. agar medium made from veal broth with the addition of 0.5 per cent. sodium chloride and 1 per cent. peptone. It should then be adjusted to a pH of 7.8, which allows for a reduction of 2 points in autoclaving, 7.6 being the desired end point. The medium is then tubed, autoclaved and slanted. After solidification the usual cotton plug is replaced by a sterile rubber cork to retain the water of condensation, and the medium keeps indefinitely. When completed and cooled some flocculation is present in the butt of the tube. This can easily be removed if the medium in bulk is placed in the autoclave, quickly brought to 15 pounds pressure, removed, filtered, tubed and replaced in the autoclave for the completion of sterilization. While this improves the appearance, it seems to make some

change in the medium which causes more scanty growths.

Blood-agar is particularly valuable for the isolation of the pneumococcus, the influenza bacillus, and members of the catarrhalis group. It is also of some value as a differentiating medium for the pneumococcus on account of the peculiar manner in which the pneumococcus colonies take up the pigment. If the colony 'fished' stood alone the resultant subculture is likely to be pure. After twenty-four hours' incubation, a microscope slide should be made from each culture and stained by Gram's method.

For a tentative diagnosis, the relations and grouping of the bacteria may be studied more satisfactorily from a bouillon culture.

This preliminary identification is generally sufficiently accurate for practical purposes. The ultimate identification and classification according to species and variety constitute a much more extensive and complicated procedure. In considering the isolated bacteria for the preparation of a vaccine, the thing of paramount importance is to be certain that they are not spore bearers. If there is any doubt upon this point it is better to omit the organism from the vaccine until a definite decision can be made, because, as the vaccines are prepared at present, the method of sterilization is not sufficient to destroy spores. Even though the check tests may be made with the greatest care there is a chance that any spores present may not find suitable conditions for rapid development, and thus escape detection.

Upon the evidence gained from an examination of the slide made from the bouillon culture and stained by Gram's method, we are able to clas-

sify the cocci with a high degree of accuracy. Gram-positive cocci in irregular groups may be considered staphylococci; the color of colonies upon agar will tell whether they are "aureus" or "albus." The *Staphylococcus pyogenes citreus* so seldom occurs that it need not be considered a distinct variety. Liquefaction of gelatin will further help to differentiate between pyogenic and non-pathogenic species. The pyogenic strains liquefy gelatin. If Gram-positive cocci occur in tetrads they are likely to be the *Micrococcus tetragenus*; the sarcina occurs in cubes or packets. Bezançon has called attention to the *M. paratetragenus*, which is said to appear on the slide as Gram-positive cocci with a background of Gram-negative cocci. Cocci occurring in chains are likely to be streptococci, although pneumococci may and often do grow in chains. The demonstration of a capsule, after passing the cultures through a mouse, and the lanceolate shape are decisive in identifying the pneumococcus. The appearance of the pneumococcus colony on blood-agar, as mentioned before, is very characteristic. Pneumococci in plain bouillon cultures are dissolved by the addition of ox-bile, while the streptococci are not. Also, unlike the streptococcus, the pneumococcus generally ferments inulin. Gram-negative cocci are likely to belong to the *Micrococcus catarrhalis* group, though they may be meningococci or gonococci. The source of the specimen aids in identifying the gonococcus, while the meningococcus is not suspected anywhere outside the spinal canal except during epidemics. It does, of course, occur in the nose and may offer some difficulty in an attempt to differentiate it from some

members of the *M. catarrhalis* group. For the further identification and classification of the "coccaceæ" the reader is referred to Winslow and Horder ("The Systematic Relationships of the Coccaceæ").

On account of their infinitely greater variety, the bacilli may not be so conveniently classified. Cultures from the respiratory passages may contain influenza and pertussis bacilli, both of which are very small Gram-negative rods with rounded ends, and of scanty growth. Larger Gram-negative bacilli, especially if they are encapsulated, are classed as members of the Friedländer group. The *Bacillus ozeana* is a member of this group. From the intestinal canal, or from lesions possibly infected from it, Gram-negative bacilli may be members of the typhocolon group, and their identification must be determined by studying their ability to ferment various carbohydrates, coagulate milk, produce inulin, etc.

*Detoxicated Vaccines.*—David Thomson (Lancet, June 28, 1919) has used  $N/10$  NaOH to dissolve gonococci, meningococci, *B. typhosus*, *B. Friedländer* and *B. influenza*. To get the Gram-positives in solution, e.g., the staphylococci, streptococci, pneumococci and diphtheroids, 15 per cent. antiformin was employed. After neutralization by hydrochloric acid the antigenic precipitate was separated. The supernatant fluid was found to contain the toxic properties.

Similarly, according to W. B. Wherry and J. A. Bowen (Jour. of Infect. Dis., Dec., 1925), *B. dysenteriae*-Shiga is detoxicated by a 1 per cent. solution of formaldehyde, as previously reported by Ramon and Dumas (Paris méd., Dec. 6, 1924). Large doses of

the detoxicated product may be injected into rabbits without harm and a potent agglutinating serum formed. Rabbits immunized in this way are resistant to doses of living bacilli which kill controls.

*Residual Vaccines.*—A modification of the Thomson detoxicated vaccines has been suggested by C. E. Jenkins *et al.* (Brit. Med. Jour., June 11, 1921). The resulting vaccines, to which the name "residual vaccines" has been given, are prepared as follows:

1. Two or 3 Petri dishes of culture.
2. 100 c.c. of 1 per cent. phenol in water.
3. Add 40 per cent. NaOH to make a 0.5 per cent. solution.
4. Set aside one hour (solution becomes clear).
5. Add strong HCl until neutral to litmus plus one drop to each 10 c.c. of fluid (solution becomes opaque).
6. Hydrogen dioxide (10 vol.), 1 c.c. to each 50 c.c.
7. Place in oven at 55° C. for 24 hours.
8. Decant supernatant fluid.
9. Add 1 per cent. phenol to original volume.
10. HCl, 1 drop to each 10 c.c.
11. Allow to sediment 3 to 6 hours.
12. Decant supernatant fluid.
13. Neutralize with 40 per cent. NaOH.
14. Make up to original amount with normal saline solution.
15. Autoclave 15 minutes (temperature 120° C.).

The 2 cardinal features which distinguish this class of vaccines are: (1) They are not rendered inert by weak solutions of oxidizing agents; (2) their toxicity is neither destroyed nor impaired by a temperature of 120° C.

The effects of the vaccine referred to in cases of **chronic bronchitis** are described as follows: (1) In most cases there is distinct improvement in the patient's general condition, color, vigor and capacity for activity. (2) The sputum, which may at first increase in amount, in practically every case diminishes in quantity and loses its mucopurulent character, becoming white and less profuse. (3) The cough becomes less persistent and the attacks or paroxysms much fewer and less severe, particularly those occurring in the night and early morning. (4) A striking feature was relief from **asthmatic attacks**; from the clinical point of view this was the most conspicuous effect produced.

#### AUTOGENOUS VACCINES,

*Preparation of.*—After the microscope slides have been studied to ascertain the absence of spores, the cultures, 18 to 24 hours old, may be used for preparation of the vaccine. About 1 c.c. of sterile normal saline solution is added to each tube and the growth is loosened and large clumps are broken up with a platinum wire. If there is a very scanty growth on the surface of the medium, as may be the case with streptococci and pneumococci, transplants should be made into fluid media enriched with sterile blood serum. Influenza bacilli should be planted on blood-agar slants which have been heated to 90° C. after the addition of the blood. Extreme care, must be exercised in planting from one tube to another, as there is the greatest possible danger of contamination. A good-sized bulb pipette is of considerable assistance for this purpose. The transfer may be made by carefully flaming the mouths of

both tubes immediately before pouring from one to the other. The thick suspension is finally transferred to an empty tube and this tube is sealed in the Bunsen or blow-pipe flame. The sealed tube is shaken vigorously for at least half an hour. The addition of a few glass beads to the tube before its sterilization has been recommended to assist the shaking process in breaking up clumps of the bacteria. If clumps persist it may be of advantage to centrifugalize the suspension for a few minutes.

*Counting the Bacteria.*—The bacteria should be counted before they are killed. Such organisms as meningococci and gonococci may liberate so much autolytic substance that many

#### Wright pipette.

of the organisms are dissolved and disappear during the sterilization. The vaccine probably does not lose any of its potency on account of this, because the autolyzed bacteria have fully as much immunizing power as have the whole germs.

The sealed tube containing the bacterial emulsion is marked with a file and the upper part cracked off carefully. A small quantity of the thick suspension is drawn up into the larger part of a sterile Wright pipette, the capillary end of which is then sealed in a small flame, thus making a tiny cup containing a sample of the suspension. The tube containing the suspension is resealed. A Wright pipette is marked with a blue-wax pencil on the capillary stem one-half to five-eighths inch from its extremity. A rubber teat is fixed on the larger end. This tube is to be

used for measuring and mixing equal parts of blood and bacterial suspension. A bandage is now wrapped around the thumb or middle finger, which is pricked just back of the nail. By gently manipulating the rubber teat, then dipping the end of the capillary pipette in the drop of blood, it is filled exactly to the mark made by the wax pencil. The end is then removed from the drop of blood, carefully cleansed, and a tiny bubble of air allowed to enter; the end is then dipped into the suspension of bacteria and a volume of the suspension equal to the volume of blood is drawn in. The blood and bacterial suspension are then forced out on a microscope slide, drawn up into the tube, and again forced out. This procedure is repeated until the blood and bacterial suspension are thoroughly mixed. Small drops are then placed on clean slides, and with the edge of a second slide the mixture is spread evenly in thin layers. The film is allowed to dry in the air, is fixed by heat or wood alcohol, and stained by methylene blue, diluted fuchsin, or Wright's stain. Under the microscope the red blood-corpuscles and the bacteria are seen evenly distributed. The number of each is counted and the figures set down in separate columns. Enough fields are counted to equal about 500 red corpuscles. The number of red corpuscles in 1 c.c. of the blood of the operator being known, and the ratio between the corpuscles and bacteria being ascertained by this enumeration, it becomes a simple mathematical problem to calculate the number of bacteria per cubic centimeter. For example, if the number of corpuscles in the fields examined equals 500 and the number of bacteria in the same

fields equals 1000, then a cubic millimeter of the emulsion contains 10,000,000 (as 500 is to 1000, so is 5,000,000 to 10,000,000). This supposes that the blood of the person making the count contains 5,000,000 red corpuscles per cubic millimeter. It is advisable to corroborate this figure by one of the well-known methods of enumerating red corpuscles.

A convenient plan for standardizing vaccines has been described by L. R. Tehon (Jour. Amer. Med. Assoc., Oct. 4, 1919). In the preparation of autogenous vaccines, the writer used, as a routine, Wright's method of counting. In so doing he experienced some little discomfort in handling the array of figures usually employed in making the necessary computations. As a short cut, the formulas here given have proved useful and satisfactory, it being entirely unnecessary to compute the number of organisms per cubic centimeter in the suspension. The result obtained gives the number of cubic centimeters of the suspension of organisms needed to make up a desired quantity of vaccine which will contain the desired number of organisms.

#### FORMULAS.

Quantity of Vaccine.	Millions of Organisms per C.c.		
	1000	500	200
10 c.c.	$\frac{1.82 \times a}{b}$	$\frac{0.909 \times a}{b}$	$\frac{0.3636 \times a}{b}$
15 c.c.	$\frac{2.72 \times a}{b}$	$\frac{1.36 \times a}{b}$	$\frac{0.5454 \times a}{b}$
25 c.c.	$\frac{4.54 \times a}{b}$	$\frac{2.27 \times a}{b}$	$\frac{0.909 \times a}{b}$
50 c.c.	$\frac{9.09 \times a}{b}$	$\frac{4.54 \times a}{b}$	$\frac{1.818 \times a}{b}$
100 c.c.	$\frac{18.18 \times a}{b}$	$\frac{9.09 \times a}{b}$	$\frac{3.64 \times a}{b}$

In computing these formulas the number of red blood cells is arbitrarily taken to be 5.5 million per cubic millimeter; "a" is the average number of red blood cells obtained from the count, and "b" is the average number of organisms.

Suppose we wish to make up 15 c.c. of vaccine which shall contain 500 million organisms per cubic centimeter. The red blood cell count we will suppose to have been 50, and the bacterial count 75. We now substitute these numbers in the proper formula as given, and have:

$$\frac{1.36 \times 50}{75}$$

which is equal to 0.9. This is the number of cubic centimeters of the suspension of organisms which, when made up to 15 c.c., will give a vaccine containing 500 million organisms per cubic centimeter.

When the exact content per cubic centimeter of red blood cells is known for the blood used in the comparison, the following formula may be used in any case:

Total number of organisms needed:

$$\frac{b}{a} \times \text{number of r.b.c. per c.c.}$$

This gives the number of cubic centimeters of the suspension of organisms in making up a desired quantity of vaccine with a desired content of organisms.

#### *Sterilization of the Thick Emulsion.*

—After the small sample has been removed for counting and the tube containing the thick emulsion has been sealed again, it is immersed in a water bath and kept at a temperature of 56° to 60° C. for from one-half to one hour, according to the variety of the organ-

isms. For killing the bacteria the tube containing the thick suspension must be *sealed* and *entirely immersed* in the water. It has been determined that if an antiseptic is added to the suspension before it is sterilized the specific proteins are altered so that the vaccine is much less potent. For this reason, the degree of heat and the length of the exposure are usually diminished to the minimum commensurate with safety. Certain organisms, such as gonococci, pneumococci, and the influenza bacilli, are sometimes not heated at all, the antiseptic being depended upon for sterilization. This procedure is not safe, however, for such vigorous organisms as staphylococci and certain strains of streptococci. After removal from the water bath, the tubes are opened for the removal of their contents and the dilution of the vaccine. Before the dilution is made, subcultures upon a suitable medium should be made to determine the sterility of the thick suspension.

*Diluting the Vaccine.*—The next step is to dilute the thick suspension sufficiently to make each cubic centimeter contain the desired number of bacteria. The diluent is generally sterile physiological saline solution (0.85 per cent. sodium chloride) containing 0.25 per cent. tricresol, 0.5 per cent. phenol, or 0.25 per cent. liquor cresolis comp. The amount of diluent to be mixed with the thick suspension in order to obtain the desired strength is a simple mathematical problem. Staphylococcus suspensions are diluted so that 1 c.c. of the completed vaccine will contain about 300,000,000 cocci per cubic centimeter and other bacteria, so that each cubic centimeter will contain about 50,000,000. These figures are arbitrary and

the strength may be adjusted to suit the individual preference of the immunizer. Mixed vaccines are made in exactly the same way except that the mathematical calculation of the amount of each thick suspension required to be added is made separately.

*Test for Sterility and Safety.*—The tests for harmlessness and sterility are of more importance than any other factor in the preparation of the bacterial vaccine. Substances intended for injection beneath the skin must be prepared with infinitely more care than those intended for oral administration. Extremely dangerous substances taken by mouth may generally be recovered or their effects neutralized by well-known means, but when a harmful or infected substance has been injected beneath the skin it is impossible to recover it. Relatively few of the pathogenic bacteria are able to resist the germicidal action of the gastric juice, but the subcutaneous tissues are susceptible to practically all of them. Our tests then must assure us that the vaccine contains no substance poisonous or harmful in itself, and they must demonstrate the absence of all living bacteria and spores.

The subcultures from the completed vaccine are therefore of paramount importance. The medium on which they are made must so dilute the preservative that its direct antiseptic action can have no influence upon the development of any living bacteria or spores that might be present. For this reason subcultures on agar or other solid media cannot be used; they must be made into a suitable *fluid* medium. Furthermore the subcultures must be made under conditions which will favor the development of anaërobic bacteria and spores as well as aërobes, because the most

### PLATE III.

Fig. 1.

**Mixing the Blood and Thick Suspension.—Right.** The two columns in the pipette are forced out on a clean slide and drawn up again into the tube by gentle manipulation of the rubber teat. This is repeated several times.

**Making the Smear upon the Slide.—Left.** After thorough mixing, a drop of the mixture is placed on a clean slide near its end. This is then spread evenly by drawing the edge of another slide over it. The smear is then fixed and stained.

Fig. 2.

**Red Corpuscles and Cocci Spread on Slides.—Microscopic examination for counting bacteria in relation to the corpuscles.**



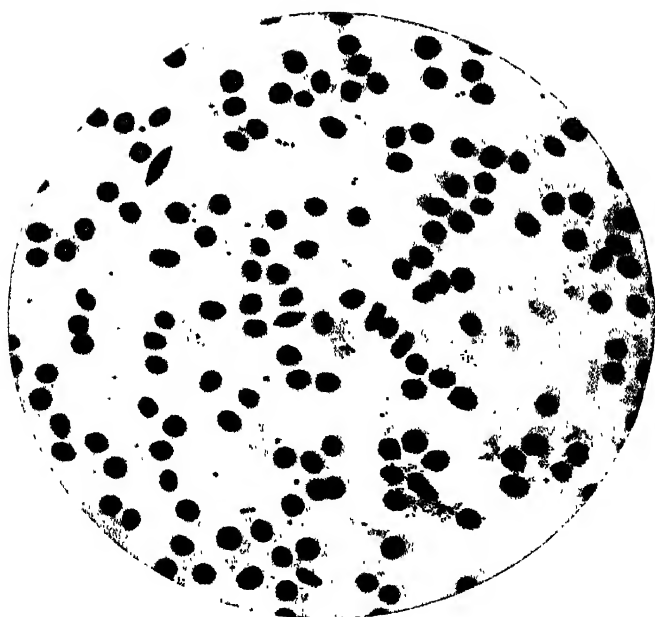
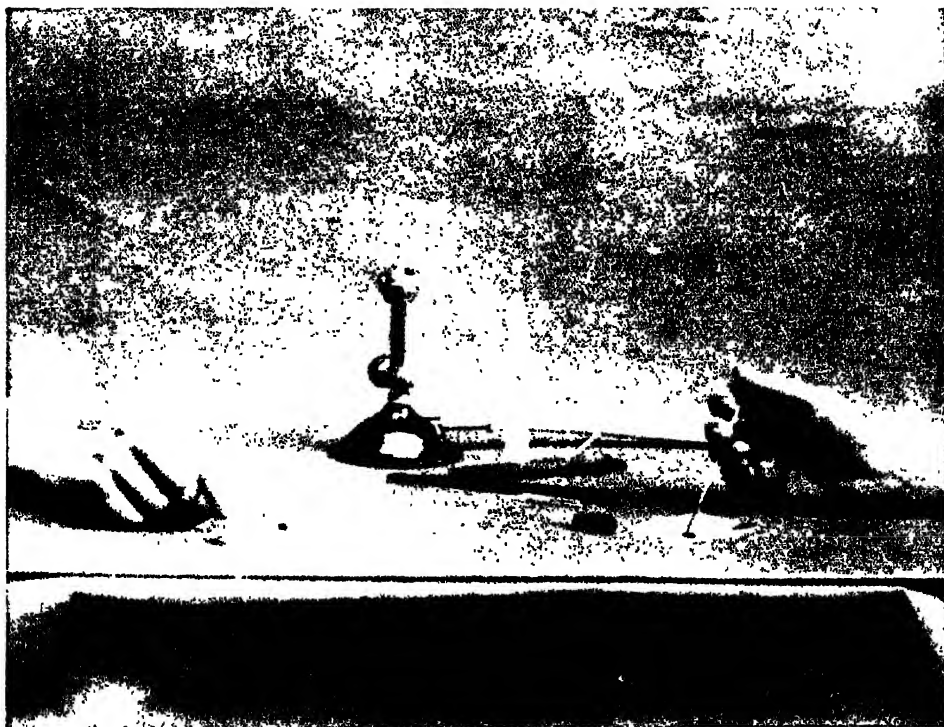
Fig. 1.

Mixing the Blood and Thick Suspension.—Right. The two columns in the pipette are forced out on a clean slide and drawn up again into the tube by gentle manipulation of the rubber test. This is repeated several times.

Making the Smear upon the Slide.—Left. After thoroughly mixing a drop of the mixture is placed on a clean slide near its end. It is then spread evenly by drawing the edge of another slide over it. The smear is then fixed and stained.

Fig. 2.

Red Corpuscles and Cocci Spread on Slides.—Microscopic examination for counting bacteria in relation to the corpuscles.





dangerous organism that may gain access to the vaccine is an anaërobe and a spore producer. This organism is the tetanus bacillus, and it is so ubiquitous that it must never be considered absent without proof. Then a culture medium in a tube or vessel which will favor the development of the tetanus bacillus should be suitable for subcultures from bacterial vaccines. Bouillon in ordinary fermentation tubes seems to answer all requirements. The tetanus bacillus will develop readily in a fermentation tube containing preferably 1 per cent. dextrose bouillon, provided it has been freshly sterilized. Under these conditions the closed arm is sufficiently protected from air to favor the growth of anaërobes.

As to whether or not tetanus spores might develop, any doubt is removed if a small piece of guinea-pig liver or heart tissue, as recommended by Theobald Smith, is crowded into the bend of the fermentation tube. The fermentation tube subcultures must be incubated at least forty-eight hours before an opinion may be given as to whether or not the vaccine is sterile. The naked-eye appearance of the tube is not sufficient, because the growth of tetanus and any flocculent material at the bend of the tube must be studied under the microscope.

*The "Short" Method.*—For reasons possibly best known to those who are engaged in such practice there has been developed a technique which is mentioned only to be condemned. This is the so-called "short" method of preparing autogenous vaccines. It may not be sanctioned except for cases such as puerperal septicemia, when it is of the utmost importance to obtain a vaccine of some kind within the shortest pos-

sible space of time. Under such circumstances cultures are made directly from material containing the infecting organism and incubated overnight. If the culture is in bouillon the bacteria are counted and the culture is heated to 60° C. for one-half hour, diluted with normal saline solution, the antiseptic added, and the vaccine used forthwith. If the culture has been made on agar the growth is suspended in normal saline solution and then treated as a bouillon culture. It is never *safe* to use a vaccine without first testing it for harmlessness and sterility, but it must be recognized that there are times when we must choose between two evils. This short method may be applicable when pure cultures are obtainable from the blood, as in streptococcus and pneumococcus septicemia, and in the cases of furunculosis, when there is only a staphylococcus present. It should not be recommended in any case where there is a mixed infection or where it is at all possible that extraneous organisms may have entered during the collection of the infected material. It should never be used for making autogenous vaccines from sputum, urine, ulcers of various kinds, or suppurating sinuses.

*Vaccine Containers.*—The most convenient container for autogenous vaccines or those made extemporaneously in small amounts is the bottle fitted with a rubber cap devised by Wright. The capacity of the bottle is from 20 to 30 c.c. It is plugged with cotton and sterilized in an oven by dry heat, the rubber cap being sterilized in the autoclave or by boiling for twenty minutes in 0.2 per cent. carbolic acid or tricresol solution. After pouring the vaccine into the bottle or running it in through a pipette the rubber cap is stretched

over the mouth of the bottle. The advantage of the rubber cap is that with a needle of small caliber vaccine may be withdrawn from the bottle without removing the stopper, thus avoiding considerable risk of contaminating the vaccine. The cap is first wiped with liquor cresolis comp. or phenol, the needle of the syringe is plunged through the rubber, the bottle is turned upside down, and the vaccine is withdrawn into the syringe. After the withdrawal of the needle the rubber closes automatically and no further procedure to protect the vaccine is necessary.

**Inoculation, Site of.**—The site to be selected for making the inoculation may be important. Acting upon the theory that opsonins are produced locally, attempts have been made, in certain obstinate conditions, to inject up-stream with regard to the focus of infection, the supposition being that the newly liberated antibacterial substances are thus carried directly to the focus of infection by the lymph as it drains through it. In this manner the antibacterial substances might be expected to come into application in a concentrated condition.

This, however, is practically not often taken into consideration. At the present time the vast majority of injections are subcutaneous into the arm near the insertion of the deltoid muscle. It is sometimes more convenient to vaccinate women in the suprascapular region because this point may be reached by merely loosening the dress at the back of the neck. Many physicians prefer the inner surface of the forearm below the bend of the elbow.

**Technique of Injection.**—It is advisable to scrub the site of injection with soap and water, followed by alco-

hol and ether, or an area of the skin about the size of a five-cent piece may be painted with pure lysol, tincture of iodine, or 5 per cent. solution of iodine in acetone. If lysol is used the excess must be wiped away after the removal of the needle.

**Reactions.**—At the point of injection there usually appears within a few hours an area of redness. This persists for twenty-four to forty-eight hours or longer, according to the size of the dose and the susceptibility of the patient. Following a very large dose some constitutional disturbance is not infrequent. This consists of pains in the back and limbs, headache, and possibly slight fever.

**Accessory Methods of Treatment.**—In the opinion of the writer the most important chapter contributed to our knowledge of therapeutic inoculation by Sir Almroth Wright is not that concerning opsonins and the determination of the opsonic index, but that concerning the methods by which such antibacterial agencies as the patient may already possess or may acquire by immunization may be used by the tissues for the destruction of microbes at the focus of infection. Not infrequently the opsonic index of the patient before treatment is as high as the immunizator may reasonably expect it to be after treatment, and yet the infection continues as though there was a poverty of bacteriotropic substances in the blood. If such occurs without vaccine inoculation it is likely that the same conditions are responsible for those cases in which inoculation fails to benefit the patient even after treatment has been continued sometimes for months. We know that the parenteral introduction of foreign proteins into animals, except in the

rarest instances, *must* be followed by the production of specific antibodies. If, then, the newly formed antibodies which the patient certainly possesses are not exerting any influence whatever upon the infectious process, the failure is due to conditions which prevent the bacteriotropic substances from coming in contact with the infective elements.

Attention called to the importance of the reticulo-endothelium in the formation of antibodies. In mice in which the reticulo-endothelium had been largely excluded by splenectomy and intravenous injection of saccharated iron, blocking the endothelium, active immunization against pneumococci often failed. F. Neufeld and H. Meyer (*Zeit. f. Hyg. u. Infekt.*, Sept. 20, 1924).

Where inoculations are undertaken for prophylactic purposes the immunizer is not required to make any disposition for bringing the antibacterial elements of the blood fluids and the phagocytes into application upon invading microbes. Exactly the same thing holds true in vaccine therapy where the bacteria have not yet effected any fundamental changes in the invaded tissues. But where they have already gained a foothold and profoundly modified local conditions the situation is entirely different. It is then necessary not only to increase and maintain the antibacterial power of the blood, but also to take special steps to bring the phagocytes and antibacterial elements of the blood into contact with the invading micro-organisms.

In the circulating blood the body has at its immediate disposal the entire bacteriotropic substances contained in the plasma as well as its whole force of phagocytes. On the contrary, when the bacteria effect an entrance into the tissues they find opposed to them only

such stray phagocytes as may be casually passing through the tissue spaces and only that amount of antibacterial substances which is contained in the lymph that flows through these particular tissue spaces. If this statement needs support it is necessary only to point out the fact that blood infections are of rare occurrence compared with localized infections, which are common. It is quite clear that the aim and object of our treatment ought to be to equalize conditions in the infected tissue and in the circulating blood.

Inflammation is evidence of an attempt to preserve the immunity of the tissues: first, by the transfer of phagocytes, and, second, by the transfer of antibacterial fluid from the circulating blood to the invaded tissues. Whenever this effort fails changes in the tissues occur which hinder the effective access of phagocytes and bacteriotropic substances to the infecting microbes. The result is the establishment of a focus of infection which is specially favorable to the invading bacteria. The impediment may consist of a defective blood-supply to the seat of infection, hypercoagulable and hyperviscid condition of the blood, accumulation of excessive fluid in the focus of infection, or plugging of the tissue spaces by accumulated leucocytes and coagulated lymph. In the latter case the gradual reduction of the antibacterial potency of the lymph renders the phagocytes ineffective and the accumulation of bacteriotoxins and tryptic ferment paralyzes them.

In the case of an excess of serous fluid about the focus of infection it is obvious that the poverty in phagocytes tends to retard the destruction of bacteria; the bacteria gradually absorb the bacteriotropic substances from the fluid,

which then becomes less potent in antibacterial power. In the reverse condition the tissue spaces are plugged with leucocytes and with coagulated lymph, in which case we have a preponderance of phagocytes over fluid elements. This hinders the conveyance of any additional lymph or of any reinforcing phagocytes to the focus of infection. When an infection goes to the point of suppuration, disintegration of the leucocytes liberates in the focus of infection increasing quantities of a tryptic ferment overpowering the normal anti-tryptic power of the lymph. The fluid pus becomes definitely tryptic and immediately surrounding tissues are rapidly dissolved, with the result that a sac is formed and definite fluctuation is obtained. It is clear that if fresh phagocytes should be brought to the scene there would be no opsonins to assist them and no benefit could result. The outflow of lymph from superficial vessels, associated with the inflammatory reaction to a superficial infection, is stanching when the lymph begins to coagulate and is definitely arrested when it desiccates and hardens into a scab. Any phagocytes which may be contained in such lymph are first immobilized and then killed by drying. On the other hand, bacteria which are not killed by drying are sheltered from the attacks of the phagocytes. These have the opportunity of multiplying in the deeper and correspondingly moister layers of the scab, where they reduce the antibacterial power of the comparatively stagnant lymph and may then be in a position to invade the underlying subcutaneous tissue or epithelium and thus extend the area of infection. In a sinus which is freely discharging pus the conditions are

similar to those in an abscess. The pus possesses a low opsonic power, it contains no effective leucocytes, it may be charged with bacterial toxins, and it contains a tryptic ferment. A sinus which is not discharging presents a condition somewhat comparable to that of a *well* in which the inflowing water has deposited on its walls an insoluble element which chokes all the conduits of inflow. Upon the walls and floor of such a well forms of life may quite well maintain themselves as they could not against a copious inflow of water. So in a dry sinus the density of the granulation tissue lining it prevents free outflow of lymph upon the surface.

There are two measures which may aid in overcoming the conditions that prevent the access of the leucocytes and bacteriotropic substances of the blood to the infecting elements. The first of these comprises those measures which may be employed to stimulate the egress of antibacterial agencies from the blood; the second, those measures which may be employed to open the way for the entrance of the antibacterial substances and phagocytes into the actual focus of infection.

An increased blood-pressure favors the egress of the antibacterial substances. Where the focus of infection is so situated that its blood-supply can be controlled the arterial circulation may be increased and the venous circulation impeded. The capillary pressure may be raised by the application of heat in any form or by rubefacients. Bier's method of applying a bandage to the limb is also advised. In dealing with the question of raising capillary pressure two considerations must be kept in view. On the one hand, the question as to whether the normal

blood-supply to the infected part is capable of furnishing an adequate lymph-stream must be considered; on the other hand, we must weigh the advantage which would be derived from the determination of increased protective substance of the infected part against the disadvantage which might result from the fact that the ampler lymph-stream would carry into the blood bacterial products which were previously locked up in the focus of infection—*autoinoculation*. In many cases this is a question which cannot be resolved without a trial supplemented by a series of blood examinations. In general it may be said, however, that the greatest advantage will be where the bacterial focus is situated in a poorly vascularized tissue and that the disadvantage will be least (*a*) in the earlier stages of an infection, (*b*) where the bacterial focus is of strictly moderate dimensions, and (*c*) where it has just been evacuated. In the case where the dimensions of the bacterial focus are considerable the disadvantages of determining an increased lymph-stream to the affected tissues will generally altogether outweigh the advantages.

Wright has pointed out that a condition of diminished coagulability is associated with increased transudation into the tissues and that a condition of increased blood coagulability is associated with restricted transudation of the lymph which is very prone to coagulate in the tissues. He has further shown that the blood may be made more coagulable by the administration of calcium salts or may be diminished in coagulability by the administration of a decalcifying agent, such as citric acid (citric acid, 2 to 4 grams, t. i. d.). These points come into application, the

former in cases where there is constant autoinoculation when the administration of calcium salts are sometimes of decided benefit. On the other hand, the administration of citric acid has proven a very important addition to the treatment of brawny swelling. Wright has placed on record the details of a case of Ludwig's angina in which citric acid was the sole remedy necessary to bring about a rapid recovery from the infection.

Among the measures which may be employed to open the way for the entrance of antibacterial elements in the focus of infection there may be considered evacuation by incision, evacuation by aspiration, evacuation by puncture or incision combined with cupping, evacuation by puncture, or incision; or removal of scabs combined with the local application of a chemical lymphagogue.

Evacuation by incision is the usual surgical procedure for the treatment of any focus of infection in which pus is present. Practically the only thing desired by the surgeon is the evacuation of the pus, and if no pus is found incision is considered useless. Notwithstanding this the chief value of the incision is that by the evacuation of the pus antibacterial agencies of the blood may be brought into effective operation upon the tissues surrounding the abscess cavity. For the incision to be of the greatest benefit, then, the opened wound should be used to induce a flow of lymph through the infected tissues.

The danger of secondary infection in an incised wound and the resultant sore would make one hesitate and attempt to find a better method for the evacuation of the pus. In general all requirements are satisfied by aspiration. An



ordinary syringe needle is inserted into the abscess cavity and the fluid pus removed. An equivalent of drainage can be obtained by repeated aspirations.

Bier and Klapp have recommended a method of evacuation by incision or multiple puncture combined with cupping. At first sight this method would seem to furnish exactly the forces any immunizator would wish to employ for evacuating the inflammatory products from choked tissues and for drawing out the blood and carrying from the infiltrated tissues a stream of immunizing lymph. One requisite to success has been overlooked. In reality this procedure is a filtration process carried out with the help of an exhaust. It will be clear that, where a viscid and coagulable fluid has to be drawn through a very fine system of pores, the clotting of the fluid in or at the mouths of these pores may very readily bring the filtration to a standstill. In the case of a laboratory experiment the filter, if it is a paper filter, will then bulge and give way. In the case of the animal tissues, in like manner, even when the negative pressure is kept within strict limits, inevitably something will give way. What will in point of fact give way will be the delicate capillary walls, and in the case of a carbuncle thus treated its last state is, according to Wright, worse than its first.

To continue with the illustration of the filter: If we can clear the surface of it (as by the removal of scabs from an infected surface) or pierce through the surface layer of the filter (as by incision or puncture into a focus of infection), and if we can then without the application of any violence cause the fluid to well out through the pores, at the same time depriving that fluid of its

coagulability, we shall then gradually open up and keep open the choked filter.

In a hypertonic salt solution containing sodium citrate we have a chemical agent which will, when applied to the surface of an open system of tissue spaces, cause a lymph-stream to flow outward through these tissue spaces toward the surface, while it will, at the same time, deprive that lymph of its coagulability. Such a solution consists of 5 parts of common salt and  $\frac{1}{2}$  part citrate of soda dissolved in 100 parts of boiling water. Sometimes a concentration of 1.5 to 2 per cent. of salt containing the same amount of citrate will be preferable. Where incisions have been carried down in the infiltrated tissues, lint soaked in the stronger solution may with advantage be put in the wounds. Sinuses *should* be syringed out with the same lotion, a piece of lint soaked in the lotion being afterward introduced into their orifices.

The skin in the neighborhood of the orifice is protected against the irritating effect of the brine by a coating of vaselin.

After a wound has in this way been sufficiently washed with a stream of immunizing lymph, it will be well to stanch the lymph-flow by powdering the surface with a styptic powder consisting of calcium chloride 1 part, precipitated chalk 400 parts.

**Dosage.**—It was first believed that one of the most important things to be settled before practitioners could use bacterial vaccines in their work was the matter of dosage. This was apparently based upon the belief that as much harm might be caused by an overdose of a bacterial vaccine as had been shown by experience to be pos-

sible from the injudicious use of tuberculin. Wright probably led in this feeling and arrived at his conclusions as a result of observations upon the negative phase. It is true that in patients who are extremely ill and suffering from conditions associated with profound toxemia or bacteremia only minimal doses should be administered; but in sthenic types of disease the greatest harm that might be done appears to be a transient increase in the severity of the local condition, with subsequent benefit. In other words, experience has shown that, in general, bacterial vaccines are harmless. Metastatic foci of infection have not resulted from overdoses, and there is no record of a single instance where serious harm has been done by the employment of bacterial vaccines.

Leary reported 2 cases which through an error received 10 billion dead staphylococci at a single dose. No ill effects at all were noticed in one; the other, however, collapsed a few hours after the inoculation, but responded to strychnine and the application of hot-water bags and had practically recovered from the immediate effects of the dose within fifteen minutes.

It is the consensus of opinion that for subsequent doses the clinical symptoms following the initial injection give a sufficiently reliable guide. The important point about dosage to be determined, then, is the size of the initial dose. As noted in the clinical section of this article, there is little uniformity in this. Dosage in America is apparently higher than in England, and in both countries the amounts given now are usually greater than the doses recommended originally by Wright. It has become

the custom to make vaccines of greater strength than formerly and reduce the initial dose to 0.1 c.c. Thus, in the case of streptococci, the gonococcus, pneumococcus and *M. catarrhalis*, vaccines containing 500,000,000 in 1 c.c. are frequently used, and in the case staphylococci, the typhoid and colon bacilli, etc., twice this strength is common practice.

The rule that appears to be very generally followed is that a patient with an acute condition must be given the smallest dose compatible with the severity of the case, while chronic conditions are treated with larger doses.

Where the dose given is followed by a systemic or local reaction it is probably too large, and the next dose may, with less discomfort to the patient, be smaller. A very slight and transient increase in the severity of symptoms, followed by improvements, is an indication that the dose has been the proper one.

**Intervals Between Doses.**—The intervals between doses are varied in inverse ratio to the size of the dose and the severity of the disease. There has been a tendency toward a more frequent administration of very small doses in acute infections. In pneumonia, erysipelas, septicemia, epididymitis, etc., amounts as small as 5 million have been given daily for several days. But this plan must be looked upon as unusual, three days being the more common interval in the acute stage, and five to seven or ten in chronic conditions. At the end of a course of staphylococcus vaccine, for instance, it is customary to give a very large dose about once a month to prevent a return of the trouble.

**PROPHYLAXIS AND THERAPEUTICS.**—The use of bacterial vaccines has assumed a place of great importance in the prophylaxis of several epidemic diseases, although developments along this line may go further.

Practical methods have been elaborated for the control of the typhoid and paratyphoid fevers, bubonic plague, and cholera.

Much good work has been done in England, chiefly by Allen, upon the prophylaxis of common colds. In this country encouraging observations have been made upon the use of meningococcus vaccine.

Along therapeutic lines, considerable investigation has been conducted with regard to vaccines against pneumonia, bronchitis, colitis, erysipelas, ozena, pertussis, various septic complications, etc.

At present no sweeping assertions can be made concerning the therapeutic value of bacterial vaccines generally, but the indications are that further progress in the treatment of infectious diseases will be made to an important extent along the lines of specific therapeutics.

For certain infections, *c.g.*, those caused by the staphylococcus, vaccine inoculation has become a routine method of treatment.

The precise function of the vaccine must be recognized. The parenteral administration of any foreign protein results in the formation of antibodies. The chief purpose of these antibodies appears to be the removal of their corresponding proteins from the tissues. To accomplish this, it is obvious that direct contact of antibody with antigen is a *sine qua non*. Types of infection in which the bac-

teria find their focus of growth in poorly vascularized tissues are therefore the most difficult to influence. Such lesions as hypertrophied tonsils or prostate may offer an impassable barrier to the body fluids.

That an accurate bacteriological diagnosis is to be made, and the homologous vaccine used, goes without saying. It appears to be the custom at present when favorable results have not been obtained with a stock vaccine to say immediately, as though there were no other possibility, that an autogenous vaccine is indicated. Possibly it is, but if the dictum should go forth, as would seem to be the desire of some writers, that autogenous vaccines should always be used, the application of bacterial vaccine therapy would be restricted to very narrow limits instead of covering the wide field for which it is appropriate.

Reports of the therapeutic use of bacterial vaccines must at present be accepted at their face value. Not a few authors seem too enthusiastic, while undoubtedly others are biased the other way. This variation represents so accurately the experience which every physician will have in his practice that it has been thought advisable, in what follows, to give abstracts and quotations from various writers rather than a general summary or expression of personal opinion.

An attempt has been made to bring out in each case the doses that have been used and the intervals between doses, so that the material presented may be of the greatest value to the physician who desires to compare his experience in relation to vaccines with that of others.

**TYPHOID FEVER.****PROPHYLACTIC INOCULATION.**

—The universal prevalence of typhoid fever renders it one of the most interesting and important of the infectious diseases from the standpoint of prophylaxis by inoculation. For many years the index of the sanitary conditions in a community has been the incidence of typhoid fever there, and sanitary measures to eliminate infectious diseases have been aimed directly against typhoid fever with the belief that, in general, sanitation which would eliminate the typhoid bacillus as a contamination in food-stuffs, potable water, etc., would go far toward the elimination of every other infectious disease contracted through the alimentary canal. That this belief is well based there can be no doubt, and, even though the employment of typhoid vaccination should become more widespread as a preventive measure, public health regulations with regard to the disposal of refuse and the protection of drinking-water, milk, and other foodstuffs must be kept up without regard to specific immunization.

Using the original method of Pasteur, Fränkel and Simonds in 1886 found that repeated, small, non-lethal doses of typhoid bacilli would afford protection to rabbits against fatal doses of the same organism. In the same year, Beumer and Peiper suggested the use of *killed* cultures for the immunization of men, but they made no investigations themselves. Several others reported work on animals, but nothing practical came of it. In 1892, Brieger, Kitasato, and Wassermann proved that it was not necessary to use living organisms, since killed cultures were equally ef-

fective. Up to this time nothing was known concerning the mechanism of typhoid immunity. But in 1893 and 1894 Pfeiffer and others, studying the changes in the bacteria when injected into the peritoneum of a guinea-pig that had been immunized to typhoid, recognized that the degree of immunity depended upon the degree of bacterolysis. In this study they injected immunized guinea-pigs intraperitoneally with lethal doses of cholera vibrios or of typhoid bacilli. In immunized animals the bacteria were found to lose their motility, swell up, become granular, and finally disappear (Pfeiffer's phenomenon), while in unimmunized susceptible animals the bacteria did not lose any of their motility, increased rapidly in number, and the guinea-pigs died with the peritoneal cavity teeming with germs. It was found later that, if the organisms were mixed with the serum from an immunized animal and the mixture injected into the peritoneal cavity, the same phenomenon took place as when the organisms were injected into the peritoneal cavity of an immune guinea-pig. This demonstrated the possibility of ascertaining the effect of the immunizing process upon an animal. The discovery of agglutinins later by Gruber and Durham and their application to clinical medicine by Widal made the demonstration of immunity easier. Sir A. E. Wright appears to have been the first to inject typhoid bacilli into men, but he did this in the course of an investigation on the coagulability of the blood and not for the purpose of producing immunity to typhoid fever. A few weeks later, in 1896, Pfeiffer and Kolle immunized two men and investigated the changes

in their blood-serum. They were thus the first to actually inoculate men for the purpose of protecting them against typhoid fever. Pfeiffer and Kolle showed that not only were agglutinins produced, but also that the bacteriolytic power of the blood was increased just as during an attack of typhoid fever.

In 1897 Wright published the results of antityphoid inoculation upon 18 men, showing that the method was practicable and gave sufficient protection to be worthy of adoption by the army. The next year (1898) Wright introduced prophylactic inoculation into the British Army in India. At first the results were not generally convincing. Much of the vaccine was probably overheated. Subsequently, Leishman heated the vaccine to 56° C. for only one hour.

So far as is known at present, artificial inoculation and accidental infection result in the production of identical antibodies. According to the observations of Firth in India, the immunity induced by antityphoid vaccination commences to recede approximately 2½ years after the prophylactic injections.

**Preparation of the Vaccine.**—The preparation of typhoid vaccine does not differ essentially from the preparation of other ordinary bacterial vaccines. For making it in large quantities, quart bottles known as Blake bottles, or a modification of them, or Roux or Kolle flasks are used. These flasks contain ordinary nutrient agar. The typhoid bacillus is grown on this agar for twenty-four hours. A small quantity of normal saline solution is then run into the flasks, preferably from a Miquel bulb, and the growth is washed from the

surface and suspended in this fluid. This thick suspension is collected from the several bottles into sterile Miquel bulbs, both stems of which are then sealed. The bulb is shaken to break up clumps, and a small quantity removed for counting, after which the bulb is again sealed and exposed to a temperature of 60° C. for one-half hour or 55° to 56° C. for one hour. Renaud has reported the use of ultraviolet rays for killing the bacilli by subjecting the suspension to the rays for thirty minutes. After the thick suspension has cooled, it is diluted with normal saline solution and 0.25 per cent. tricresol is added as a preservative. Dilutions are made so that the material for the first dose will contain 500 million killed bacilli per c.c., and for the second and third doses 1000 million per c.c.

Wholesale vaccination of the troops at the front during the World War was commenced in February, 1915. Between 1911 and the breaking out of the war 20,000 men of the French Army had been vaccinated against typhoid and paratyphoid A and B with mixed or triple vaccine; 200,000 others had been vaccinated against typhoid only (H. Vincent). Thanks to this active immunization, these diseases could be considered as having been practically vanquished. From 7.24 in December, 1914, per thousand men, the number of cases dropped to 1.6. In August and September, 1915, the morbidity (paratyphoid predominating) rose to 2.47 and 2.65, but then it diminished steadily. In February, 1916, the percentage of cases per thousand was less than 1. In 1917, the rate dropped to 0.063 per thousand. Vaccination by 2 injections was responsible for this remarkable recession in the number

of cases and deaths, and the mortality then fell so low that one was obliged to evaluate on the basis of 0.3 per 100,000.

According to Russell, there were in two years during the World War 1065 cases of typhoid fever among the approximately 4,000,000 vaccinated men of the United States forces, *i.e.*, one case to every 3765 men, as against one to every 7 men in the Spanish-American War. The deaths from typhoid amounted to one to every 25,641 men, as against one to every 71 in the earlier war. Vincent calculated that among the French troops over 1,000,000 cases of typhoid and 145,000 deaths from it would have occurred during the war had not vaccination been practised.

Prophylactic typhoid vaccine may be said to be as certain as that against small-pox; serious untoward effects are very rare, and it is the duty of physicians to demand vaccination of all classes against typhoid fever.

The vaccine is administered by subcutaneous injection. The skin may be scrubbed with soap and water and finally rinsed with alcohol and ether as for an ordinary operation. Practically no untoward results have followed the simpler method of painting the skin with liquor cresolis comp. or iodine. An area about the size of a five-cent piece is painted with tincture of iodine or liquor cresolis comp., and the needle is plunged directly through this painted area. Upon the withdrawal of the needle the excess of liquor cresolis comp. is wiped away with a piece of clean cotton. Injection of the vaccine intramuscularly possesses no advantage over the subcutaneous method and appears to give rise to more pain and incon-

venience. The procedure is best carried out in the afternoon, as a general reaction will be less noticed during the period of sleep.

**Local and General Symptoms Following the Injection.**—The symptoms following the injection of antityphoid vaccine are similar to those following the injection of other vaccines. The process cannot be considered entirely painless or indifferent, and there should be no attempt on the part of the physician to conceal the fact that there will be some local, and possibly a general, reaction. For the benefit of those who suffer considerable local pain, it may be remarked that it is believed that, the more severe the local reaction, the higher will be the resulting immunity and also the longer will be its duration.

Fifteen minutes to three hours after the injection, the local reaction commences. It is characterized by some pain and redness, heat, and finally slight swelling of the skin, the area of which may equal that of the palm of the hand. This is somewhat edematous and more or less painful upon pressure, or when the limb is moved. There may be a slight febrile reaction. Following the second inoculation the same train of symptoms may be noticed, but they are more rare and generally less severe when they do occur. The third inoculation is generally accompanied with little discomfort. Among those inoculated in the United States Army there have been found a few very susceptible individuals, but the number of severe reactions has been small, and, regardless of their severity, they have disappeared in forty-eight hours.

The condition of the body determining whether the reaction will be

severe or moderate is as yet not well understood. Those presenting severe reactions who have not had typhoid undoubtedly present the least resistance to the disease when naturally infected.

In District No. 2 of the Canadian Army between January 1, 1915, and January 1, 1917, 58,382 men were inoculated 3 times each, making in all 175,146 inoculations. They had no deaths from these inoculations, and there were admitted to the hospital for this cause only 117 cases, less than  $\frac{1}{4}$  of 1 per cent. of the men inoculated, or about 1 admission to every 1200 inoculations.

Russell states that, as a rule, there is a red, tender spot about as large as the palm of the hand at the point of injection, making its appearance six or seven hours after injection and reaching its full development in about twelve hours. After this it gradually disappears and has entirely subsided in forty-eight to seventy-two hours. Occasionally the local reaction is somewhat more severe; the lymph-glands may become slightly swollen and tender to pressure; however, local applications have never been necessary, and in no case has suppuration developed. The general reaction varies in its symptoms. In children and in many adults it can be said to be absent. In its milder form it causes a transitory headache and a feeling of malaise which lasts from two or three hours to a day. Slightly more marked general reactions are evidenced by considerable headache and a decided feeling of lassitude. Occasionally there are chilly sensations without much rise of temperature. A few have complained of nausea and a very few of diarrhea lasting a day. The men described

their condition as "I thought I was going to have a cold," "a sore throat," or "an attack of grippe." Moderate reaction is characterized by a rise of temperature to 101° to 103° F. A few had bad chills. Severe reactions are those showing temperature 103° F. and more. They complain of chills, more or less headache, nausea, vomiting, or herpes labialis; no case of albuminuria has been reported.

Russell has recorded detailed statistics concerning the percentage of reactions of various grades. In the administration of 128,903 doses in adults there occurred "mild" general reactions in a percentage diminishing from 28.9 after the first vaccine injection to 20.3 after the third; the corresponding percentages for "moderate" general reactions were 2.4 and 1.5, and for "severe" reactions, 0.3 and 0.1. In children the general reactions were much less frequent after the 2d and 3d injections than in adults.

According to Leishman, the negative phase in typhoid vaccination is a negligible factor. There is no increased susceptibility immediately following inoculation (Russell).

In answer to the question: Should antityphoid vaccination be done during an epidemic of typhoid fever, Heger and Mockel have described an epidemic which occurred in the insane hospital at Wiesloch, of which they vaccinated all the inmates and personnel (1500 persons in all). Among the 129 cases of typhoid that occurred, the proportion of serious cases before vaccination was 44 per cent. and among vaccinated subjects, 23 per cent. Eight subjects were vaccinated during the incubation of their typhoid, the disease running a normal course with, perhaps, a lower temperature than

usual. No complications were observed and the epidemic was, in fact, nipped in the bud. Therefore the reply to the question submitted is affirmative.

It has been claimed that antityphoid inoculation renders the recipient more susceptible to tuberculosis or tends to activate latent tuberculous foci; but according to Russell, tuberculosis in the Army not only did not increase after the introduction of vaccination, but actually decreased.

Clovis and Mills (Jour. Amer. Med. Assoc., Jan. 31, 1920), recording experiences as to the effects of typhoid vaccine on pulmonary tuberculosis, state that 62 tuberculous patients were given typhoid vaccine, comprising 9 incipient cases, 24 moderately advanced, and 29 far advanced. In the series, 37 cases were active and 25 inactive. Only the active cases gave severe reactions, and there were no permanently bad effects.

Stefansky observed that on an average 1 out of every 400 or 500 men vaccinated against typhoid showed considerable disturbance. The temperature ran up to 102° or 104°, with vomiting, diarrhea, jaundice, transient albuminuria and syncope. The symptoms disappeared within a couple of days.

In a man of 30, alluded to by Benon (Rev. de méd., Oct.-Nov., 1922), antityphoid vaccination was followed by depression and weakness and later by hypersthenia and mania. Cases of asthenia after vaccination are rare, and a predisposition to it must be present.

Tanabe (Mil. Surg., Jan., 1923) observed that seventeen out of twenty-six soldiers who reacted comparatively seriously to antityphoid immunization had previously been recorded as exhibiting signs of status lymphaticus.

In an ophthalmologic service where 22,000 troops were vaccinated against typhoid, Bussy (Lyon méd., Jan., 1919) saw 5 men who developed ocular lesions thereafter. Two of the men had kidney disease, but it was latent and difficult to detect. After the vaccination, 1 developed albuminuric retinitis and died of uremia 2 months later. He was a man of 45. This suggests the advisability of testing the blood-pressure as well as examining the urine before vaccinating against typhoid. The other patient presented severe hemorrhages in both retinas after the typhoid vaccination. The 3 other men developed herpes and ulcerations of the cornea, but recovered without impairment of vision.

**Determination of the Efficiency of the Inoculation.**—The introduction of the typhoid antigen into the body brings about the production of defensive bacteriotropic substances. These are agglutinins, lysins, amboceptors, and opsonins. The exact practical indication of an estimation of these various antibodies has been a matter of considerable discussion and investigation. The larger doses of vaccine usually, but not always, give the highest agglutinating, bactericidal, and bacteriolytic titres, and it is believed that the agglutinating power of the serum is of great importance in the valuation of the vaccine. According to Hachtel and Stoner, because of the great variation in individual susceptibility, there is no correspondence between the size of the dose and the amount of the reaction, nor between the severity of the reaction and the amounts of antibodies produced. The French Commission concluded that antibodies are constantly present, though vari-



able in quantity. Pfeiffer, Kolle, Hetsch, and Kutscher called attention to the lack of constant correlation. Notwithstanding this, the phenomenon of agglutination has become the method of choice for the diagnosis of typhoid fever, although it may not always give an accurate estimate of the value of the vaccine and the degree of the immunity of the person vaccinated.

Concerning experience in the laboratory of the Army Medical School, Russell stated: "We have examined the blood-serum of a large number of vaccinated persons and have invariably found evidences of immunity. The test for agglutinins is made by the macroscopic method, and the serum dilutions are prepared with great care. The increase in the agglutinins is evident by the sixth or seventh day, and the rise in opsonins follows quickly. The Widal is positive in high dilutions of the serum, in many cases being present in a dilution of 1 in 5000 to 10,000 or even 1 in 20,000. Only rarely does it fail to rise above 1 in 500 or 600. It reaches its maximum soon after the third dose and falls rapidly at first and then more slowly toward normal. In a few of the cases examined it is found to have reached normal within a period of six months, but oftener has remained present for nearly a year.

"The leucocyte count is temporarily, but regularly, raised after each dose of vaccine. The rise is often to 15,000, but it soon begins to decline and reaches normal in about ten days."

Protection of guinea-pigs against death from typhoid bacilli through the bacteriolysins and agglutinins in human serum before and after anti-

typhoid vaccination has been studied by B. Tanabe (Mil. Surg., Jan., 1923). The bacteriolysins were found increased about 400 times in most cases by the vaccination, and the agglutinins 20 to 40 times. The serum drawn on the seventh day after the second injection of vaccine already contained a tolerable amount of the protective antibodies. The protective value of the serum was considerably decreased one year after the inoculations, but it was still five times greater than that of normal serum.

*Contraindications* to antityphoid vaccination comprise menstruation, advanced nephritis, acute infections, and active tuberculosis (unless a typhoid epidemic exists).

**Practical Results of Prophylactic Antityphoid Vaccination.**—The literature which has accumulated concerning the prophylactic value of typhoid vaccine is voluminous and overwhelming in establishing the efficiency of this measure from a practical standpoint.

The *length of the period* of complete protection is generally admitted to be about one year, though partial protection may last much longer.

Typhoid vaccination is compulsory in the American Army. Many hospitals require all internes, nurses, and other attaches, especially those coming in contact with patients, to be vaccinated against typhoid fever. The Samaritan Hospital was the first in Philadelphia to establish this rule.

The serum gives a positive agglutination reaction in every one who has been vaccinated against typhoid, according to Ascoli. The diazo and chromogen reactions, the leukopenia and aneosinophilia are also the same in the typhoid patient and in those merely vaccinated against typhoid.

Cultivation of typhoid bacilli from the blood and bile (after ingestion of oil) and the hemolysis test are the main reliances now for differentiating typhoid patients and detecting carriers. If the bile is added to bouillon containing serum known as agglutinate typhoid bacilli, if typhoid bacilli are present in the bile they will be agglutinated in clumps in 6 hours.

After antityphoid vaccination immune substances can be found in the blood for a varying time, sometimes for several years, and after they have disappeared the individual responds more quickly to another inoculation. According to A. Fleming it has been observed in the British army in India that while in the preinoculation days the most dangerous period, as regards typhoid, was the first year of the soldier's sojourn, the maximum incidence now is in the third year. This seems to show that the immunity conferred by the vaccine lasted at least 2 years.

Yagisawa stated that during the period between the war with China and the war with Russia (1897 to 1903), the morbidity averaged 5 per thousand of the average force of 125,629 Japanese troops, with a mortality of 1 per thousand. Then the morbidity increased to 8 and the mortality to 1.3 per thousand. Antityphoid vaccination was then introduced, in 1908, and the morbidity dropped to 0.7 and the mortality to 0.08 per thousand among those vaccinated more than once, while the figures remained at the same height among the non-vaccinated and the civilian population. Intestinal hemorrhage occurred in only 6 per cent. of the 266 vaccinated typhoid patients and in 16.4 per cent. of the 122 non-vaccinated.

Chantemesse, referring to the French Army in the third year of the World War, pointed out that there were only 136 cases with 7 per cent. mortality among the 80,000 men who were vaccinated, while there were 525 cases with a mortality of 14 per cent. among 60,000 not vaccinated. These figures included both typhoid and paratyphoid. Only one fatal case of typhoid occurred in a man who had been completely vaccinated, and in this case staphylococci were isolated from the meninges. Three of the fatalities were from paratyphoid.

The following conclusions regarding vaccination against the typhoid group of infections have been endorsed by H. J. Nichols and C. O. Stimmel (*Jour. of Exp. Med.*, Sept., 1923): A high immunity can be obtained by a sufficient vaccination, but can be overcome by a large enough infecting dose. Repeated doses give better immunity than a single dose. Frequent courses probably give the greatest protection. According to Army regulations, vaccination is given every three years. Maximum immunity lasts about eight months. Typhoid vaccine alone gives no adequate protection against infections with paratyphoid A and B.

**Typhoid Fever after Prophylactic Inoculation.**—A number of cases of typhoid fever were reported by C. P. Brown, F. W. Palfrey, and L. Hart (*Jour. Amer. Med. Assoc.*, Feb. 15, 1919), which began to appear about the end of June, 1918, among troops stationed at Camp Greene, N. C. Of the cases reported 12 had previously received the full dosage of antityphoid vaccine, 2 recruits had each received 2 doses of vaccine, 2 had received a single dose each, and 2 had not been

inoculated. A mild epidemic of typhoid occurred concurrently in Charlotte, the nearest city to the camp, and infection was thought by the health authorities to be fly-borne. As this mode of infection was not considered probable in the camp, careful investigations were made in regard to the milk, water, and ice used, but no particular information was elicited. Cultural examinations were made of the blood, urine, and feces of the 18 cases reported; the blood was positive in 13 cases, or 72.2 per cent.; the urine, in the same number of cases, and the feces, in 9, or 50 per cent. Cross agglutination tests showed wide variation, both as regards individual strains and the preparation of the agglutinating fluid by different methods, thus demonstrating the desirability of using standard agglutinating fluid for Widal tests. The results of these tests also strongly suggest that the same method should be used in checking the agglutination of patients' serum with the homologous strain. The authors concluded that occasional cases occur in which the usual preventive inoculations against typhoid fever fail to protect against the disease, most probably on account of the ingestion of virulent organisms in massive doses.

**Therapeutic Value.**—Much work has been done at various times with regard to the specific therapy of typhoid fever. Among the first to investigate in this direction was Fraenkel. Chantemesse also attacked the problem from another standpoint, using a serum. The results obtained by Chantemesse were unique. No other observer has been able to obtain results comparable to those reported by him, and a careful perusal of the

papers published by Chantemesse makes one wonder whether some error had not modified the figures intended for publication. A number of years ago various substances were used for the treatment of typhoid fever by M. W. Richardson at the Massachusetts General Hospital. Richardson concluded from the use of vaccines, split products (Vaughan), and serums that these methods of treatment did not reduce the mortality; that they did not shorten the course of the disease, but that relapses were apparently less frequent, and also that some of the patients were probably more comfortable than if they had not received such treatment.

Occasionally the treatment of the disease by bacterial vaccines, and serums as well, is attended by brilliant results.

Results obtained in military practice in Serbia with vaccine treatment in typhoid fever have been reported by Petrovitch (*Bull. de l'Acad. de méd.*, June 13, 1916). Whereas, among 1020 cases treated by ordinary measures the mortality was 12.8 per cent., among 2270 other cases subjected to vaccine treatment, without the administration of cold baths, it was only 2.7 per cent. Small doses—5 to 50 millions of typhoid bacilli killed by heat—proved as efficacious as larger ones. Where results were slow in appearing, and in complicated cases, the dose was reduced rather than augmented, and such reduction proved essential for benefit in these patients. Very toxic cases, often in subjects greatly exhausted and already weakened by dysentery or cholera, proved in no way refractory to the treatment except when the eliminatory functions were impaired. A few of these patients, however, died in con-

valescence, rather from extreme cachexia and anorexia than from myocarditis. In cases with renal or myocardial complications, and in general when elimination is in abeyance, the writer counsels great reduction in the dose, lest uncertain or even unfavorable results ensue. The dose in general should be based, first, on the rule that all pronounced local and general reactions are to be avoided, and second, on the general progress of the case, in particular the temperature, with due attention to the functions of the liver, kidneys, skin, respiratory apparatus, and intestine. Small doses are of advantage in avoiding excessive excitation of the tissues as well as an excessive production of antibodies, with resulting massive liberation of endotoxins and stress on the eliminatory organs. The habit was formed of giving a little **caffeine** internally after the second injection.

Anders treated 8 typhoid-fever patients with small doses of typhoid vaccine. In this series, in all save 1 of which the Widal reaction was present, no reactionary fever occurred, but in two instances the nocturnal remissions became distinctly greater immediately after the use of the vaccines. The injections seemed sufficiently powerful to cause a gradual decline of temperature to normal in the course of several days. Anders concluded that typhoid vaccine has a place in suitable cases when continued during convalescence, to prevent relapse; to combat local infections with the typhoid bacillus, as, for example, bone suppurations which arise in the period of convalescence, and for the removal of the typhoid bacilli from the feces and urine in typhoid carriers.

Callison has used an initial dosage of 500 million, repeating the injections at intervals of four days and increasing the dose 100 million at each subsequent injection. He collected statistics of 323 cases of typhoid fever treated with vaccines, which showed a mortality of 5.2 per cent. This compared favorably with the 16 per cent. reported by Bellevue and allied hospitals.

On the other hand, a careful comparison between cases treated by usual methods and an equal number treated by vaccination does not seem to have shown that the latter merited greater confidence than the former under similar conditions of nursing, food, etc.

In 15 typhoid cases reported by K. D. Fairley (*Med. Jour. of Austral.*, Nov. 12, 1921), however, 8 were given vaccine intravenously and 7 served as controls. The average febrile period was shortened by  $10\frac{3}{4}$  days in the treated cases; half of these cases and one relapse were aborted by crisis. In both mild and severe cases the diminution of the toxic features was striking. The dull, apathetic patient of the second or third week was converted within 48 hours into a bright, alert, hungry individual. There is no advantage in the procedure unless instituted early. An initial dose of 150,000,000 bacilli, increased to 250,000,000 on subsequent occasions if the reaction has been mild, is advised. The vaccine is given daily for 4 to 6 days. Contraindications are hemorrhage, pneumonia, myocardial degeneration and meningeal symptoms.

According to G. S. Bel (*New Orl. Med. and Surg. Jour.*, Apr., 1923), the use of a sensitized vaccine may shorten the course of the illness, prevent relapses and sequels, and may preclude the possibility of a recovered patient becoming a carrier. He advises, however,

against giving the vaccine after the first week, and especially during the third week of the disease. The first dose is about 10,000,000 killed bacilli, and the injections are repeated at intervals of three days until three to five doses have been given.

**Bacillus Carriers.**—Several workers have described successful results from the use of vaccines in the treatment of typhoid carriers.

Irwin and Houston, *e.g.*, reported the case of a typhoid-bacillus carrier treated with vaccine. The typhoid bacillus was found in the urine, but not in the feces. The blood gave a typical Widal. The initial dose of 50 million bacilli caused a rise in temperature for a few days. A week later, injection of 100 million was followed by less marked disturbance. The urine was examined as before, and the colonies which developed on the Petri plates were much fewer than on previous occasions. Two weeks later 200 million were injected. The urine examined after this inoculation showed as many typhoid germs as before. The patient was put on sodium lactate to make the urine alkaline, and three weeks later an injection of 300 million was given. No typhoid bacilli could be found in the urine after this injection. Two weeks later an injection of 500 million was given, and four weeks afterward 1000 million were injected. No bacilli could be found in the urine or feces. The Widal reaction was still marked. The patient had increased markedly in weight, and her general condition had returned to normal.

Goubau studied the question in 30 convalescent carriers treated with autogenous vaccine or a Wright monovalent vaccine in weekly injections. The

bacilli disappeared completely in 2 months in all of the 23 thus treated during the first 5 months after the disease. The bacilli disappeared from convalescents given the vaccine treatment much earlier than in those not thus treated. The effect was prompter, the shorter the period after defervescence when the autogenous vaccine was commenced. After an interval of 5 months no appreciable effect was apparent in 43 per cent. of the cases. When the interval had been only 2 months, 6 carriers were cured with 3 injections; 3 with 4, and 2 others with 5 and 6.

Goubau also studied the persistence of bacilli in 431 persons of all ages and both sexes who had been vaccinated once against typhoid and 246 unvaccinated. Of this total of 677, 14.33 per cent. still harbored typhoid, but the vaccinated got rid of them sooner than the unvaccinated, although the difference was not marked. None of the vaccinated were carriers of typhoid bacilli beyond the seventh month, while they were found up to the sixteenth month in 0.43 per cent. of the unvaccinated. No carriers of paratyphoid A were found after the fifth month or of B after the seventh.

Clements and Dawson have also reported on the treatment of a chronic typhoid carrier with specific vaccine. The man received six injections of vaccine, starting with 125 million and increasing up to 600 million, over a period of four months. An attack of cholecystitis developed, but disappeared without other treatment. Although the last attack of hepatic colic occurred one month after the last injection, typhoid bacilli could no longer be isolated from the feces. The case was interesting as being the first re-

corded cure of a gall-bladder carrier. As to whether the treatment by vaccine was the cause of the attack of cholecystitis they are unable to give a definite opinion. It is, however, certain that the cholecystitis was the immediate cause of freeing the gall-bladder of all foci of the infection.

Brem and Watson, reviewing literature, found 11 recoveries of chronic typhoid-bacillus carriers, 5 of whom recovered during vaccination with autogenous vaccines. Their own patient was a child of 4½ years. Shortly after her attack of typhoid fever her father and mother were infected. Typhoid organisms in pure culture were isolated from the child's urine. Methenamine had been administered to the patient during two weeks of convalescence from the typhoid attack. Practically the only treatment given was vaccination with autogenous vaccines. Nine doses were given, increasing from 25 to 1500 million. The bacilli decreased gradually, and disappeared after the ninth vaccination. Eleven successive urine cultures were positive for *B. typhosus* and then five successive cultures were negative. The total duration of the bacilluria, from the time of normal temperature, was about six months. The patient appeared to be a continuous carrier. It seemed that the disappearance of the bacilli was not an intermission but a true recovery, brought about by the gradual healing of a chronic lesion under the influence of vaccination.

J. P. Watt (Lancet, Feb., 24, 1923) reported the case of a woman who had been a carrier for 18 years and given rise to several typhoid outbreaks. A detoxicated vaccine was given subcutaneously at 5-day intervals, the dose in thousand millions being 1, 2, 4, 6, 8,

10, 12, and thereafter rising by additions of 1000 millions each time to 30,000 millions. After the first three injections there was always some local reaction, and the arms were used alternately. After six months of treatment the bacillus in the stools was but feebly motile. After a temporary cessation of injections on account of a very severe local reaction, they were resumed, together with oral use of 5 minims of a standard suspension (100,000,000,000 per c.c.), gradually increased to 2 drams a day, with 2 grains of oxgall. The stools ten months after beginning of treatment were negative, and yielded 17 successive negative in the subsequent four months.

**Paratyphoid Bacilli.**—Two important organisms similar in many characteristics to the typhoid and colon bacilli are the paratyphoid bacilli. There are two of these—paratyphoid A and paratyphoid B. Paratyphoid B is more closely related in its cultural characteristics to the typhoid bacillus, while paratyphoid A stands closer to the colon bacillus. Both are pathogenic and may cause a condition clinically identical with typhoid fever. The symptoms are not often severe, and the death rate is low. The diagnosis may be made by blood-culture or by the agglutinin reaction. Of conditions diagnosed as typhoid fever, from 3 to 10 per cent., according to the locality, are in reality caused by one of the paratyphoid bacilli. When the agglutinin reaction is persistently negative with typhoid bacilli and the clinical diagnosis is typhoid it is advisable to try the agglutinin reaction with typical paratyphoid cultures.

Although paratyphoid B infections are more common, the A type has

also caused epidemics. Both have caused epidemics of food poisoning.

In view of the prevalence of infection due to the paratyphoid bacilli a prophylactic vaccine containing both the typhoid and the paratyphoid bacilli is indicated. It has been found repeatedly that immunity to typhoid fever has no influence upon the susceptibility of the individual to infection with the paratyphoid bacilli. As a combined vaccine, Widal and Salimbeni have employed a simple suspension of typhoid and paratyphoid A and B bacilli killed by heat in 9:1000 saline. The vaccine contains 10 billion germs to each 3 c.c. This is injected, first 1 c.c. and then 2 c.c. after a 7-day interval. Nearly 5000 persons thus vaccinated showed no more reaction than with the weaker vaccines, while the antibodies in the blood were later found as abundant as in those given the usual 4 doses.

A triple vaccine (T A B) is now in general use. As a rule, each cubic centimeter of it embodies 1,000,000,000 typhoid bacilli and  $\frac{1}{2}$  this number of each of the paratyphoid organisms. The first dose is 0.5 c.c., and the 2d and 3d, 1 c.c. The intervals between injections should be not less than 7 days, otherwise the degree of immunity obtained may be lessened. In children the dose is adjusted according to weight. Rest of the subject during the 24 hours following injection is advisable.

**Isolation and Identification of Typhoid Bacilli.**—Various laboratories have developed their own methods for isolating typhoid bacilli from blood, feces, and urine, but the general principles at the base of them all are the same. If the specimen is blood, some enriching method is used; if feces, the material must first be diluted in sterile broth or salt solution. Such

a dilution of feces or urine may first be inoculated into an enriching medium, as broth or bile medium, and incubated, or it may be immediately streaked upon a differential medium, such as the Conradi-Drigalski or the Endo medium. Characteristic colonies are fished after twenty-four hours and final diagnosis made, including agglutination tests with a specific immune serum of high titre.

The modified Endo medium devised by Kendall and Day has much to recommend it. It contains 15 grams of agar per liter, instead of 40, which results in the development, after eighteen hours, of larger and more distinct colonies than appear in 40-gram agar. The second point of divergence from the original is in the reaction, which is made just alkaline to litmus instead of being strongly alkaline to it, so that those bacteria forming acid have less alkali to neutralize and show their characteristic changes very quickly.

F. F. Russell proposed a double sugar tube medium, the use of which he interposes as a step between the use of a modified Endo medium and the agglutination test. Typhoid-like colonies fished from Endo streaked plates are inoculated upon these tubes, on which the reactions of typhoid, paratyphoid, dysentery, and coli are very distinctive. Growth upon tubes showing characteristic typhoid reaction can be used for macroscopic agglutination test. One great advantage derived from the use of this medium is the elimination of a great bulk of the work involved in testing for agglutination, all typhoid-like colonies appearing upon the Endo plates.

The medium advised by Russell is a litmus agar containing glucose, 0.1 per

cent., and lactose, 1.0 per cent. It is slanted and inoculated by a combined streak and stab. As described by Russell, "The entire point of the medium rests upon the difference in the changes produced by the growth of the typhoid bacillus under aerobic and under the imperfect anaerobic conditions found in the butt of the tube, where the bacillus obtains its oxygen by breaking down the glucose with the liberation of considerable acid; on the surface, however, in the presence of free oxygen, no acid is formed."

The characteristic appearance of various organisms commonly isolated from feces are as follows:—

*Typhoid bacillus*: on the surface, a filiform, colorless growth on a blue background; the upper part of the tube is unchanged in color, but the lower part, the butt, is a brilliant red.

*Colon bacillus*: growth accompanied by a large amount of acidity and gas.

*Alkali formers*: no change in the medium, or slight increase in blueness.

All *dysentery bacilli* produce reactions similar to that of typhoid except that the quantity of acid is less and reddening occurs usually only along the line of the stab.

*Paratyphoids* (no distinguishing characteristic mentioned by Russell for differentiation of A and B types): upper part of medium unchanged, surface growth like typhoid, slight amount of gas as well as reddening in the butt.

Slow *colons* simulating *paratyphoids* may be eliminated by agglutination tests.

Emphasis should be laid upon the fact that all readings of reactions in this medium should be made early. Russell gives eight to eighteen hours

as the period of characteristic reaction. After twenty-four hours there may be a change in appearance due to spread of the growth or diffusion of the acid or alkali formed. This is particularly noticeable in the case of typhoid cultures. If the medium has been freshly slanted so that it is still moist when inoculated, the surface growth becomes heavy and spreading, with a consequent production of a large amount of alkalinity. After several days this may spread downward into the medium.

#### **Mixed Infections in Typhoid Fever.**

—Prophylactic results are in such marked contrast to those obtained in *treatment* with vaccine that an interesting problem is presented. Treatment is occasionally attended with brilliant results. There is, however, apparently no uniformity in this, and up to the present no one has been able to make any prediction as to whether a certain case might respond to the vaccine or not. In seeking an explanation the pathogenesis of the disease must first be considered. The *Bacillus typhi* of Eberth gains entrance to the body through the alimentary canal. The chief site of the local lesion is in Peyer's patches of the intestine. These begin to swell on about the ninth day and finally, at the beginning of the third week, break down to form ulcers. Up to about this time there is a bacteremia. But as the disease progresses cultures from the blood become more difficult to obtain. With the development of the rose spots the organisms apparently disappear from the blood.

It is safe to say that 75 per cent. of patients do not enter before the beginning of the third week, and at the time when ulcers have developed



or are about to develop in the intestine. The bacilli have disappeared from the blood and the condition of the patient is no longer due solely to infection with the typhoid bacillus. The pyogenic and possibly some of the saprophytic bacteria present in the intestine find a suitable culture medium in and about the ulcers, so that at this time the typhoid bacillus is only one of the several factors continuing the infectious process. For the successful and consistent specific therapy of the disease, then, it will be necessary to ascertain what organisms are responsible for the mixed infection and to use a vaccine containing these bacteria.

This is not an easy task. Blood-cultures are of no avail because at this period the blood is generally sterile. It is probable that the organisms in question are represented in the feces, but there must be many others which take no part in the infection and some of those desired may be killed off by the time the bowel contents are evacuated. To collect and select the proper ones from this source is likewise attended with difficulty. Some work has been projected in which the organisms isolated from the feces will be checked up against complement-fixing and agglutinating substances in the blood-serum.

If this method fails the suggestion does not seem irrational to isolate from typhoid feces representative types of well-known pyogenic bacteria, and to test these out therapeutically—in such small doses, of course, that no harm will be done the patient even if no benefit accrues.

In its later stages typhoid fever is in reality a mixed infection; the chief function of the typhoid bacillus is ex-

ercised in preparing certain tissues for various other organisms, and for this reason the specific therapeutics of the disease by typhoid vaccine alone is of limited value. Those patients in whom positive results have been obtained with it are in all probability cases in which there has been very slight or no ulceration of the intestine.

Furthermore, the uniformity of symptoms both subjective and objective and especially the blood picture strongly suggest that the mixed infection is not a haphazard one, but that it is due to certain pretty definite types. The types of bacteria associated with the typhoid bacillus may very likely determine the severity and the outcome of the disease. It is entirely possible that perforation of the intestine may be peculiarly favored by the association in the mixed infection of some organism like the streptococcus.

#### **PNEUMOCOCCUS.**

The pneumococcus is the chief cause of typical lobar pneumonia. Consolidation may also be due to certain other organisms such as the bacillus of Friedländer and the streptococcus. **Pleurisy, pericarditis, empyema, peritonitis, otitis media, conjunctivitis, serpiginous ulcer, metritis and pyosalpinx, abscesses, septicemia, and pyemia** may all be due to the pneumococcus.

For the isolation of the pneumococcus, agar containing blood or blood-corpuscles is the medium of choice. If the sputum has not been collected with great care it is better to rinse little masses of it in sterile salt solution before making smears upon the plates. The pneumococci appear as small colonies considerably pigmented

and by transmitted light very much darker than the other colonies. In isolating the pneumococcus from sputum, one may possibly obtain avirulent strains from the throat rather than the strains from the lungs. If the strain causing the disease is virulent this difficulty may be obviated by injecting the sputum subcutaneously or intraperitoneally into a rabbit (a mouse is frequently as satisfactory). The rabbit generally dies within twenty-four hours if at all, and pure cultures may be obtained from the heart's blood.

In addition to these methods blood-culture has been recommended. Blood-cultures are generally successful only in the early stages of the disease, however. If great care is used lung puncture may be made without the slightest harm to the patient. But this method may also fail. It has an advantage in common with blood-cultures in that, with careful technique, any growth occurring is likely to be pure and may be of service in a minimum length of time for the preparation of an autogenous vaccine. If the bacteria are isolated from the sputum the danger of getting avirulent strains from the throat must be taken into consideration and it is a question as to whether such a vaccine will be more useful than a good polyvalent stock vaccine.

Washburne and Eyre in 1899 first called attention to the fact that there are apparently several distinct types of the pneumococcus. This observation was later confirmed, and there were isolated distinct types of the pneumococcus none of which are capable of stimulating in a treated animal the production of antibodies antagonistic to any of the others.

For this reason stock vaccines, which must be used in the majority of cases of lobar pneumonia, both on account of the time required to prepare the autogenous vaccine and also for reasons of economy, should be polyvalent; that is, they should contain all the types of pneumococcus known, or at least the more common ones.

In a series of 60 cases in a base hospital, studied by G. F. Dick (Jour. Amer. Med. Assoc., May 25, 1918), the pneumococcus cases formed 48 per cent. of the series; of these, 21 per cent. were Type I, 34 per cent. Type II, and 45 per cent. Type IV. Only one Type III case was observed. In 46 per cent. of the cases streptococci were the predominating organisms; of these 46 per cent. were non-hemolytic. In the cases coming to necropsy the pneumonia in which this type of organisms was found resembled the ordinary pneumococcus lobar pneumonia.

**Vaccine Treatment of the Pneumonias.**—In 1912, Sir A. Wright undertook some investigations for the purpose of testing the value of bacterial vaccines in the prophylaxis and treatment of the disease. These investigations were carried on in the South African gold and diamond mines. The results of these investigations (finally reported in *Lancet*, April 13, 1918) were valuable, as the remarkable reduction in the mortality of pneumonia among the native mine-workers fully demonstrated.

F. S. Lister found that the pneumonia prevalent among the workers in the diamond mines at Kimberley, South Africa, was due mainly to three groups of pneumococci, and that "three subcutaneous inoculations with the triple vaccine of the three groups

prevent the occurrence of pneumonia as caused by members of these groups, but not the pneumonia due to other groups of the pneumococcus." From 7 to 10 million of pneumococci were given at each injection, the cocci being first killed by a germicide and not by heat. He also found that his own serum, following vaccination, contained agglutinins and opsonins against the type of organism injected, eight months after the last inoculation.

Various other investigators have reached similar conclusions.

Cumming, Spruit, and Lynch have advised vaccination of measles patients found to be hemolytic streptococcus carriers, and also advise vaccination against the streptococcus irrespective of measles patients, because the hemolytic streptococcus is of such universal prevalence that such vaccination would protect against the infection. If this procedure were carried out, they hold, the case rate, as well as the mortality of the pneumonias, both pneumococcus and streptococcus, would be reduced by a large percentage. They suggest the use of a triple vaccine consisting of the hemolytic streptococcus and pneumococcus Types I and II.

E. C. Rosenow, of the Mayo Foundation, reported results in the treatment of 200 cases of pneumonia with a partially autolyzed pneumococcic vaccine, and recommends that a polyvalent vaccine prepared in this manner be injected in all cases of lobar pneumonia as soon as the diagnosis can be made.

Mixed vaccines were opposed for a time by some of the specialists in vaccine therapy, and likewise the use of stock vaccine, but later investigations removed much of the prejudice. Castellani was one of the first to em-

phasize the importance of mixed stock vaccines. Not only did he advise the use of mixtures of typhoid and paratyphoid, but also suggested the addition of the microbes causing cholera, plague, and Malta fever. He furnished data to show that agglutinins developed in the serum as a result of the inoculation of such mixed vaccines were not less than when the vaccines were given separately.

Although this applies to diseases other than the pneumonias, it emphasizes the value of polyvalent vaccines, a fact confirmed by many observers. Bearing directly on pneumonia, however, is the testimony of S. Solis-Cohen, who states that at Fort Oglethorpe, A. Dare and D. H. Bergey treated pneumonias with a mixed vaccine, and in over 100 cases of lobar pneumonia the death rate was less than 6 per cent. Stewart recommends:—

1. Antipneumococcic and antistreptococcic serum conjointly, employing a polyvalent serum, assuming that the patient is probably suffering with a mixed infection. 2. A polyvalent vaccine made from as many strains or types of the pneumococcus and streptococcus as it is possible to obtain; preferably a sensitized vaccine, because the first step in the immunizing process has already been accomplished outside of the patient's body. The immunizing response is then more rapid and complete, while there is less likelihood of severe reaction.

W. E. Robertson, C. P. Brown, and A. G. Beckley tried serobacterins intravenously in a series of cases. Of 11 cases, some received a polyvalent bacterin composed of sensitized pneumococci alone, others a mixture of sensitized pneumococci, streptococci and staphylococci. Those receiving the

mixed bacterin reacted with a chill and a rise in temperature. Of the 11 cases, 10 ended in prompt recovery. The eleventh died of nephritis.

Mixed serum and vaccine treatment has been employed by D'Oelsnitz and Colle (*Bull. Soc. méd. des hôp. de Paris*, June 7, 1923) in 75 cases. Usually they inject 30 to 40 c.c. of anti-pneumococcus serum on the first three or four days of the disease. Treatment with a vaccine containing pneumococci, streptococci and staphylococci is sometimes begun concurrently with small doses of 100,000,000 bacteria, cautiously increased every day up to 500,000,000, after which the interval is lengthened to two days and the treatment kept up persistently to prevent relapse. An attempt is made to avoid local or general reactions. In mild cases, serum alone is used, while in spreading cases vaccine is added in small doses, and in protracted cases in large doses. These authors claim that vaccine reactions are attenuated by the previous use of serum. Among 32 children treated their mortality was 28 per cent., but of 25 adults only one died. In general, the course of the disease was favorably influenced, and relapse and complications were rare.

According to Kolmer, vaccine therapy may be of distinct aid in **delayed resolution**. He prepares autogenous vaccines of pneumococci, streptococci and staphylococci, mixed in equal numbers, from the sputum. Each cubic centimeter contains 2,000,000,000. The initial dose is 0.1 c.c., and later injections are given at three- to five-day intervals in increasing amounts.

#### **Pneumococcus Antibody Solution.**

—Pneumococcus antibody solution is

a suspension of the pneumococcus protective antibody in a slightly alkaline salt solution. It is obtained by dissociating the antibody from its attachment to sensitized pneumococci. A potent anti-pneumococcic horse serum is added to pneumococci of the three fixed types, and the bacteria absorb the antibody from the serum. The sensitized organisms are washed free of serum and the antibody is then removed by treatment with alkaline salt solution. After a process of purification, the solution is filtered through earthenware candles to insure sterility.

The solution contains from 0.1 to 0.15 per cent. of organic solids, as compared with the 8 per cent. content in serum. The potency, however, is equal to that of serum. Antibody solution contains so little serum that in some 800 treated cases no serum sickness was seen, nor did anaphylactic shock occur.

The therapeutic usage of these solutions has passed through three stages.

The intravenous use of antibody solution, as reported by Cecil, Larson, and Conner in over 500 cases of lobar pneumonia treated, showed a distinct reduction in mortality. These cases comprised lobar pneumonias of Types I, II, III and IV. The most striking effects were in early cases, Cecil reporting over 100 cases treated before the end of the third day with a mortality of 13 per cent. as compared to 26 per cent. in the control untreated series.

The antibody solution, as originally prepared, caused on intravenous injection a so-called "foreign protein shock," with chill, fever and sweating. Subcutaneous injection of the antibody was then employed, in order to avoid the shock feature. The series of cases referred to showed that this

route was not suitable and it was abandoned (Cecil and Baldwin).

Subsequent work developed a method of producing antibody solutions for intravenous use in which the shock factor was almost totally eliminated. Under these circumstances any effect produced must be attributed to antibody action. Sufficient evidence is now at hand to show that the shockless antibody solution is a powerful therapeutic agent when used early in Types I, II, III pneumococcus pneumonias, but has little effect on the Type IV group—a result to be expected.

The results, as a rule, are not as dramatic as with the original material, but usually consist in a marked drop in temperature, pulse, and respiration produced without a general reaction and with the effect of turning a severe case into a mild type.

All those who have worked with this substance insist on the necessity of early treatment; cases which are started after the third day show little change, whereas very early cases may occasionally be aborted.

Another feature which deserves consideration is the prophylactic use of this material, particularly in the aged with severe bronchitis in whom it is feared pneumonia will develop.

The introduction of this solution has allowed for the first time the use of antibodies as therapeutic agents without the accompanying dangers produced by the other serum constituents.

In a severe case of **pneumococcal meningitis**, A. C. Brown had excellent results from the use of a stock pneumococcus vaccine. Lumbar puncture showed a thick, opaque fluid with pneumococci. In all, 5 doses were given, and complete recovery of the patient followed.

**Prophylactic Vaccination Against Pneumococcus.**—A definite immune response has been secured to Types I and II, and little or none to Type III in persons vaccinated against the pneumococcus. It remains to be determined how long this immunity persists.

At Camp Upton, as reported by Cecil and Austin, 12,519 men were vaccinated against pneumococcus Types I, II and III. Three or 4 doses were given at intervals of 5 to 7 days.

During the 10 weeks that elapsed after the vaccination, no cases of pneumonia of these 3 types occurred among the men who had received 2 or more injections of vaccine. In a control series of approximately 20,000 men there were 26 cases of pneumococcus Types I, II and III pneumonias during the same period. The incidence of pneumococcus Type IV pneumonia and streptococcus pneumonia was much less among the vaccinated troops than among the unvaccinated.

Small sterile infiltrations, disappearing spontaneously, occasionally follow the injection of large doses of pneumococcus vaccine. The persons who develop these lesions exhibit local reactions to each dose of vaccine. They also give abnormally marked reactions to intradermal injections of pneumotoxin. They do not, however, exhibit anything notable in the agglutinative or protective powers of their serums after vaccination. Whereas the immune response is characteristically specific for the type of pneumococcus, this reaction is not specific for any type. The writers found no evidence that Type III is more prone to elicit these severe local reactions than are Types I and II. Prophylactic vaccination against pneumococcus of Types I, II and III is

practical and apparently gives protection against pneumonia produced by these types.

Brown and Palfrey (N. Y. Med. Jour., Aug. 23 and 30, 1919) immunized 2029 colored troops at Camp Greene, N. C., in Oct., 1918, shortly after the influenza epidemic made its appearance in camp. The lipopneumococcus vaccine was supplied by the Army Medical School. This vaccine was prepared from the three fixed types, representing ten billion of each of the three types. Only one injection was given. Of the total strength, 55.4 per cent. were inoculated and 44.6 per cent. not inoculated (control). Sixty-five cases of pneumonia occurred between the time of the first inoculation and up to the time of complete demobilization, 51 among the controls and 14 among the inoculated, 11 of the latter occurring on or before the tenth day after inoculation. No deaths occurred among the 14 cases, while there were 3 deaths in the uninoculated group.

In the 1918 epidemic of **influenza** the development of bronchopneumonia was associated with such a high mortality as to be the cause of a panic which, according to E. A. Fennel, was evidenced in the use of a variety of unjustified therapeutic and prophylactic measures. The investigations into the organisms associated with the development of the serious bronchopneumonia agreed in showing the almost constant presence of pneumococci of the fixed and heterogeneous types, and of streptococci. The possibilities of prophylaxis resolve themselves into the prevention of the pneumonia. The work of Dochez and his associates in America, and of Lister in South

Africa, proved the efficacy of prophylactic vaccination against Types I, II, and III, against which practically complete protection is obtainable. Such inoculation also gives some measure of protection against the heterogeneous types and against the streptococci, probably by virtue of the introduction of foreign protein.

Cecil (Medicine, Nov., 1925), summarizing the literature on immunization against pneumonia, found the evidence conclusive that in adequate dosage, immunity can be conferred at least against the fixed Types I, II and III. He was able to immunize monkeys by intratracheal injections of pneumococci, and suggested the possibility of producing immunity in man by means of a vaccine spray from an atomizer administered frequently during the winter months.

Various fractions of pneumococci have been used experimentally, among them Warden's lipid fraction and Perlzweig and Steffen's digest, claimed by these authors to give protection.

In prophylactic pneumococcic immunization the doses of bacteria employed are much greater than in the corresponding antityphoid procedure. Each cubic centimeter of the polyvalent vaccine may embody 8000 millions of pneumococci, consisting of one-fourth each of the four types of the organism. The initial dose is commonly 0.5 c.c. and the other two doses, 1 c.c., these injections being given at intervals of seven to ten days. The reactions are, in general, similar to those experienced after antityphoid injections.

**Empyema.**—Mixed infections are a very common cause of empyema, although the exciting cause may have been the pneumococcus. The other

organisms found are streptococcus, staphylococcus, the *Bacillus coli*, and sometimes the *Bacillus pyocyaneus*. Other organisms are found less frequently. In view of this fact, it would seem advisable, in a case where surgical interference is necessary, to attempt to raise the patient's opsonic index by the use of a mixed vaccine before the operation.

Floyd and Worthington have reported positive results in the treatment of empyema. Five hundred million pneumococci were given to 1 case. Improvement was noted. In three weeks the sinuses were almost closed and soon after the child was sent to the country entirely cured. Ross had a similar experience. In less than two weeks the discharge had entirely ceased and the sinuses completely and permanently closed.

Pastore (Jour. Amer. Med. Assoc., from *Pediatrics*, Sept., 1918) tried diplococcus vaccine in 8 cases of protracted pneumococcus infectious processes, pyothorax, interstitial pneumonia or migratory pneumonia. Acute pneumonia runs too brief a course for vaccine therapy to display much efficacy, but in these practically chronic cases the pneumococcus lesions in the pleura or the parenchyma of the lung were favorably influenced by this systematic intravenous vaccine therapy. The results were particularly striking in purulent pleurisy. The vaccine seemed to arrest the process and it retrogressed, obviating the necessity for operative measures and even puncture. The little patients were 18 months, 2 and 4, to 9 years old. The vaccine was a suspension of a twenty-four hour culture of Fränkel's diplococcus on a hemoglobinized culture medium. The bacilli were estimated by the opacity of the

fluid, and from 0.10 to 0.20 c.c. was used containing from 10,000 to 20,000 of the microbes. Up to 11 injections were made in some of the children.

#### **STREPTOCOCCUS.**

Streptococci, after the staphylococci, are among the most widespread pathogenic or semipathogenic organisms. They are frequently the cause of pyogenic infections and are very common as accessory organisms in many mixed infections. They may cause inflammation and suppuration in any part of the body. Severe grades of anemia are also associated with some streptococcal infections, undoubtedly due to a hemolytic substance which is one of the metabolic products of the growth of certain types of this organism.

Great difficulty in the clinical use of antistreptococcic serums and vaccines is caused by the existence of an almost infinite variety of types within the genus. A serum or stock vaccine prepared with one variety may have no effect in the treatment of a condition caused by another one. Experience has shown that stock streptococcus vaccines are at best valuable only as a temporary measure until an autogenous vaccine can be prepared. That the serum has antistreptococcal power can be readily demonstrated by animal experimentation and by bacteriotropic methods. In streptococcal infections of very severe grade with much toxemia it will probably be advisable to try injections of large doses of the serum first or in conjunction with the vaccine.

Many attempts have been made to classify streptococci by various methods according to morphology, cultural characters (especially in bouillon), staining properties, serum reactions, ability to hemolyze blood-corpuscles, pathogenicity for laboratory animals,

and, finally, ability to ferment various sugars.

The first work done with streptococci based upon their chemical powers or metabolic reactions was that of Merwyn H. Gordon (Lancet, p. 1400, Nov. 11, 1905). He used 33 chemical substances, out of which he finally chose 9 which he considered of differential value. These are spoken of as "Gordon's tests" and include litmus milk, neutral red agar, and broth containing 2 per cent. of, respectively, saccharose, lactose, raffinose, inulin, salicin, coniferin, and mannite.

Laboring under the belief that Gordon's tests were, to a large extent, empirical and arbitrary, Andrewes and Horder proposed a classification based on the consideration of the sum total of biological characters, including Gordon's tests. Their chief guide in determining the essential characters of various groups was the numerical frequency of occurrence of the different types.

It is well known that, in a single strain, neither the hemolytic property nor the length of chain is a fixed character. Although there is a distinct tendency toward the continuance of a certain appearance on poured blood-plates, still there is a slight unaccountable variability besides that due to recognizable difference in medium. In length of chain also, as in hemolytic power, a certain culture may show a *tendency*; but, as Andrewes and Horder have themselves pointed out, "In one and the same culture chains of the most varying length may be found; the length of the chain may vary according to the chemical composition of the medium in which the coccus grows, and may vary on subculture."

It has been observed that the differ-

ences among streptococci are not constant in relation to definite diseases. Hence, there have arisen designations relating to general properties of certain groups of the organisms, *e.g.*, *Streptococcus hemolyticus*, referring to the streptococci which are capable of causing hemolysis. These are by many regarded as identical with the original *Streptococcus pyogenes* of Rosenbach. According to Dochez, Avery and Lancefield, there are at least 4 separate types of *S. hemolyticus*, as revealed by agglutination and other tests. *Streptococcus viridans* refers to a distinct kind of streptococci which do not hemolyze but produce methemoglobin, while *S. nonhemolyticus* produces neither hemolysis nor methemoglobin.

In plating out the infectious material it must be remembered that there may be more than one type of streptococcus present and several typical colonies should be fished from the plate.

The etiological rôle of streptococci in relation to certain diseases seems in a fair way to be definitely established, as shown by the work of Dick and Dick and Dochez in scarlet fever, and undoubtedly this list will be added to as biological technique is perfected. Noteworthy is the presence of one or more members of the *Streptococcus viridans* group in tonsillitis and dental infections in which there is an arthritis and other evidences of effects of toxins rather than a distribution of the organisms. The proof of their relationship seems to be almost within our grasp.

**Local Infections.**—Beebe and Medalia have reported a case of **abscess** in the neck due to streptococcus which they treated with vaccine. Two doses of 50 million each were



necessary to effect complete cure. At the time of the first injection the patient was weak, exhausted, pale and emaciated, and suffering considerable discharge from the wound. A week after the injection the discharge had ceased, and the wound was nearly closed. A week after the second injection the wound was entirely healed, with no induration around it. Four weeks later the patient was entirely well. Good results have also been recorded by others.

In streptococcic **adenitis**, streptococcus pyogenes vaccine is recommended.

Vaccination against infection of **wounds** has been advocated by Biełonovsky, upon noting a favorable effect in wounded men treated with injections of Wright's vaccine to protect against streptococcus infection.

In the treatment of **war wounds** with a sensitized autogenous vaccine, lipovaccines and ether-sensitized vaccines, at the Virval Belgian ambulance, in charge of Professor Depage, the efficacy of the vaccine was shown most conclusively, according to C. Levaditi (Presse méd., Jan. 30, 1919). In wounds of soft parts known to be infected with streptococci and requiring further operative measures, after the vaccine had been given, the healing occurred smoothly without infection in 95.5 per cent. of the cases, as against 93.5 per cent. successful cases among those known to be free from streptococci. Generally, from 20 to 60 days in the graver cases are required before the wound can be definitely sutured. The dose of vaccine is 0.5 or 1 c.c. injected into the deltoid muscle and repeated every 5 or 6 days on alternate sides. The sensitized vaccine is prepared from 24-hour broth cultures of hemolytic strep-

tococci. The culture is centrifuged, treated with ether-chloroform mixture, and the latter decanted after 12 hours. The bacteria are suspended in saline and then antistreptococcus serum is added. The organisms are removed by centrifugation and finally the sediment is suspended in saline solution. The intradermal test proved very instructive, the reaction being found most pronounced in the cases tending to healing, testifying to a vigorous defense on the part of the organism. In the cases of grave septicemic infection there was little or no local response to the intradermal test.

In **infected gunshot injuries** of the shoulder and elbow **joints**, Swan regularly gave an injection of a mixed polyvalent streptococcus and proteus vaccine.

According to E. Breitkopf (Beitr. z. klin. Chir., cxxxiv, 145, 1925), autogenous vaccine therapy is especially suitable in **chronic sepsis** with recurrent chills and fever; **phlegmons** not running a very stormy course; **recurrent abscess** formation; **infected operative wounds**, and **chronic cystitis**. The bacteria are cultured from wound secretion, pus, blood or urine, made into a standard solution in saline, killed by heating for one hour at 56 to 60° C., tested for sterility and diluted to 1:10, 1:100 and 1:1000 in suspensions containing a little phenol. Beginning with the most dilute suspensions, the dosage is increased rather rapidly, anaphylaxis being guarded against by skin tests with 0.1 c.c. of each solution. Where there is a very strong positive response, caution at first is required, but the amount can then be increased more rapidly than in feeble patients with high fever and a weak skin reaction.

**Erysipelas.**—Harris in 1908 reported on the use of streptococcus vaccine in a case of erysipelas. At the time of the first inoculation (the sixth day of the disease) the patient was very seriously ill, with a temperature of 105.4°, pulse 140, and respiration 45. A crisis was precipitated by the injection and fourteen hours later the temperature dropped to 98.8°.

Three cases of erysipelas similarly treated were reported by Duncan and Illman. Only one dose (30 to 60 million) was given in each case. In the first case, one of facial erysipelas, fall of temperature occurred twelve hours after the inoculation. In the second case the injection, administered on the third day, when the patient's condition was becoming worse, caused rapid improvement. The third patient had inflammation following tonsillitis and spreading rapidly over the chest and arms, causing a temperature of 105.2°. Within twenty-four hours after the injection the temperature dropped, reaching a point almost normal on the third day, and normal on the fourth.

Schorer reported 37 cases of erysipelas treated with streptococcus vaccine. The dose varied from 25 to 100 million. In cases receiving the smaller dose desquamation appeared three days after the injection. Those receiving 100 million showed desquamation in two and one-half days. Three patients died of complications. In the other cases the vaccine seemed to cause shortening of the course of the disease and improvement of local conditions.

Ross has reported 50 cases in which vaccine treatment was administered. Though blood examination was necessary in certain severe cases,

he considered it unnecessary to make an autogenous vaccine in every case and recommends the use of a stock vaccine made from several different strains and as many different cases as possible. Repeated injections of 5 to 20 million streptococci were given every second day till a week after the temperature had reached normal and the erythema had subsided. Injections were given at a distance from the inflammatory area. They lessened the severity of the disease, prevented spreading of the lesions, and hastened recovery.

Walters used both autogenous and polyvalent stock vaccines in 30 cases of erysipelas and concludes that they hold an important place in its treatment by shortening the duration and preventing recurrence.

From their work on rabbits Gay and Rhodes (*Jour. of Inf. Dis.*, Aug., 1922) have shown that by graded intrapleural injections of certain streptococci, given first as vaccine, then in small amounts of living culture, the animals can be protected against multiple fatal doses given pleurally, and also against intradermal erysipelas. They feel that there is local immunity rather than a general immunity. Again, Rivers (*Jour. of Exp. Med.*, Feb., 1925), producing lesions in rabbits by intradermal injections, was able to show that animals receiving such injections developed some degree of immunity.

According to Crendiropoulo (*Jour. of Trop. Med. and Hyg.*, May, 1924), erysipelas is due to a filtrable virus, but streptococci play some part through a symbiosis.

**Chorea Minor.**—Camisa (*Cent. f. Bakt.*, Dec. 31, 1910) believed that streptococcus was the causative factor

in certain cases of chorea minor studied by him. The type found was a diplo-streptococcus, appearing in short chains, of constant morphological and cultural characteristics. The numbers present appeared in inverse ratio to the severity of the symptoms, and the blood of the patients showed agglutinating properties for it, not absolutely specific but greater than for the ordinary pyogenic streptococcus.

C. Floyd (Jour. of Med. Research, May, 1920), in studying the relationships of endocarditis, articular rheumatism and chorea, reported 20 cases in which materials collected from the tonsils and the spaces between the gums and the teeth showed streptococci. Blood cultures were all negative. Animal inoculations were made with the streptococci. Striking results followed the removal of the suppurating teeth, but neither immune serum nor autogenous vaccines produced any results.

**Septicemia and Endocarditis.**—The results of vaccine treatment in various types of septicemia and endocarditis have been generally favorable. Of course, this has been particularly true when it has been possible to use autogenous vaccines.

Callison has reported a case of streptococcus mixed septicemia clinically resembling typhoid fever. The blood-culture showed a pure growth of *Streptococcus mucosus*. An autogenous vaccine was prepared and an initial dose of 400 million given. Three additional doses of 800 million each given at intervals of forty-eight hours resulted in a normal temperature, and the patient made an uninterrupted recovery.

W. H. White described an instance of remarkable cure in a case of **septicemia**. The patient was a woman, aged

30. Severe septicemia developed rapidly, with arthritis in many joints, and constantly high temperature, following upon a small scratch on the hand. There were various swellings about the body. One was incised and a culture of *Streptococcus pyogenes* isolated from the serum that oozed from the incision. Injection with a vaccine prepared from this culture was followed within forty-eight hours by a drop in temperature. There was no further rise and recovery was complete.

Des Voeux described a case of **middle-ear infection** which he had attended. The patient was a boy who had had successive attacks. There was a clear discharge from the ear, which yielded a pure growth of streptococcus. An autogenous vaccine was prepared and administered to the patient. The patient thereafter remained well two and a half years to date of report.

In 50 cases of **septicemia** observed by Abderhalden antistreptococcic serum proved unavailing. Autogenous vaccines were then tried in 13 in addition to the regular treatment; 7 of these patients recovered.

Latham has published a long-standing case of **bronchiectasis** in which large amounts of evil-smelling pus were expectorated daily. At the time vaccine treatment was started the lungs were too badly affected to be cured. But the expectoration lost all odor, becoming bronchitic in character, and the patient was able to return to her work.

Crofton (Jour. of State Med., Mar., 1924) regards as a fallacy the view that active immunization is unsuitable in acute infections such as septicemia and pyemia. Such immunization, in fact,

gives dramatic results in the most acute septicemias, in puerperal fever, wound infections, acute peritonitis, pneumonia, meningitis and acute pyelonephritis. Active immunization is impossible, however, if the resistance of the endothelial cells of the blood-vessels is overcome and the tissues are incapable of response, as in overwhelming hemorrhagic types of infection or toward the end of a chronic infection.

Thompson used streptococcus vaccine with effectiveness in several cases of septicemia. Of 7 cases of **septic endocarditis** 3 were cured, the type being one in which he had never before seen recovery take place. In other cases which ended fatally, due to complications such as tuberculosis or pneumonia, there was evidence that the septic process had been checked by the vaccine. There was some improvement, such as fall in temperature, in all cases in which homologous vaccines were used. Several patients who came under treatment after months of illness, and in whom a fatal issue seemed imminent, gave signs for many weeks of arrested progress of the disease.

Rosenow believes that the continuation of the infection in chronic infectious endocarditis is due largely to a process of immunization and adaptation of the bacteria to the antibodies of the host. He has found that the bacteria grow more readily in the patient's serum than they do in normal serum. When they are grown in the patient's blood or serum they acquire a resistance to phagocytosis and a resistance to intraphagocytic destruction.

D. D. Browne (Med. Jour. of Austral., Sept. 13, 1924) obtained good results from autogenous vaccines in 18 cases of rheumatoid ar-

thritis, bacterial asthma, chronic pyelitis, recurrent throat infections and nasopharyngeal catarrh. In a case of subacute bacterial endocarditis, however, there were no results.

### **Septicemia, puerperal.**

Stoner, collecting the reports of various physicians concerning the results of the use of vaccines in the treatment of this condition, found 87 cases, of which 74 were reported cured, 4 improved and 8 not benefited.

Hartwell, Streeter, and Green treated 97 cases of sepsis with bacterial vaccines. Bacteriological examination was made first in all cases. There were 24 cases of general infection, 18 of which were puerperal, and 41 cases of local sepsis (25 streptococcic). All of these cases recovered.

In the treatment of puerperal sepsis Van Cott has especially recommended the use of polyvalent vaccine containing streptococci, staphylococci, and colon bacilli. Results from the use of this are very good in the majority of cases and much time is saved which would be wasted if vaccine treatment were withheld until an autogenous vaccine could be prepared.

Lloyd treated with a mixed streptococcus and staphylococcus vaccine 2 cases of puerperal sepsis, found to be infected with both types of organisms. In the first patient treatment was commenced on the eighth day after delivery. On the fortieth day, the patient was sufficiently improved to leave the hospital. The two species of cocci were found in a culture from the uterus in the second case. The uterus was then swabbed with 2 per cent. formalin and packed with iodoform gauze. Since, instead of improving, the patient's condition

became worse, an injection of 100 million cocci was given. This was followed by satisfactory progress.

Beruti used an extract of colon bacilli in a number of serious cases of puerperal septicemia, with constantly unfavorable results, the intense reaction that followed the intravenous injection being unmistakably deleterious.

He notes, however, that vaccines made with other bacteria have proved unexpectedly effectual in the hands of some, especially in Argentina, while Werner of Vienna has reported excellent results with a colon bacillus vaccine in puerperal fever.

Watters and Eaton have reported on the treatment of 50 cases of puerperal sepsis with vaccines. A polyvalent vaccine was used as soon as diagnosis seemed definite and until the autogenous could be prepared. There were 41 recoveries. Of the 9 deaths 7 were practically inevitable when treatment was commenced; one died following operation, the other after transfusion.

Western investigated 100 cases of puerperal septicemia in a special ward at the London Hospital. Some cases in which a stock vaccine was first used showed no improvement after several injections, but at once responded by a marked fall in temperature when the autogenous vaccine was given. In this series of cases, of the 56 treated 30 lived, a mortality of 32 per cent. Of the 44 cases untreated 20 lived, a mortality of 55 per cent.

Louros (Med. Klin., Mar. 4, 1923), on the basis of 2500 cases, advocates immunization of pregnant women 20 and 10 days before expected parturition with 25,000,000 and 50,000,000 streptococci. Whereas, in a hospital at Athens, 1 per cent. of unimmunized

women developed sepsis, no generalized infection developed in any of the 2500 women thus vaccinated. Of 8 cases of streptococcus sepsis and 3 of staphylococcus sepsis given autogenous vaccine intravenously, all recovered. Saidl (Casop. lek. cesk., Aug. 29, 1925) prefers polyvalent immunization one month before term.

**Scarlet Fever.**—Much work has been done to prove the etiological relation of the streptococcus to scarlet fever. The later investigations have seemed definitely to establish the possibility of prophylactic inoculation against scarlet fever.

Gabritschewsky in 1905 reported success from the prophylactic use of a vaccine prepared from bouillon cultures of tonsillitis and scarlatina streptococci killed by exposure to 60° C., 5 per cent. phenol being added as a preservative. The vaccination was to be practised only on healthy persons. The doses, graded according to the strength of the vaccine, approximated 0.3 c.c. for a patient 2 to 5 years of age, 0.5 c.c. for one 5 to 10 years of age, and 0.7 c.c. for one 10 to 15 years of age. Gabritschewsky claimed that three doses sufficed to establish an immunity against scarlet fever which would last six to eighteen months. Many Russian physicians following his methods claimed to have accomplished wonderful success in controlling epidemics.

Di Cristina (Pediatria, July, 1918) prepares the vaccine from an extract of the scales, an antigen having been found in them which seems to be able to confer permanent immunity. He dissolves out the antibodies, soaking the scales in serum from convalescents. Subcutaneous injection of this vaccine induces the production of a specific

amboceptor for the alcoholic extract of the desquamated scales. This showed that the reaction observed was not a simple reaction of the lipoids contained in the scales, but due to the presence of antigens. Children from 2 to 9 years old, treated with the vaccine until the immunity reaction appeared, in close contact with scarlet fever patients or with peeling convalescents, never developed scarlet fever.

L. Spolverini (Policlinico, Sept. 14, 1919) reviewed the use of vaccine prepared by Di Cristina's method in 10 children who were exposed by contact, wearing the clothing of scarlet fever patients. None developed the disease.

Moody and Irons (Jour. of Inf. Dis., Oct., 1920), studying the stools of 85 scarlet fever patients, found hemolytic streptococci in 30. Bliss (Bull. Johns Hopk. Hosp., xxxi, 173, 1920) found hemolytic streptococci the predominant organism in all individuals examined, when the throat cultures were made early in cases of scarlet fever. The cultures were shown to belong to a distinct biological group in agglutination reaction, absorption tests and protective power. These special characteristics of streptococci from scarlatinal sources have been abundantly confirmed. Bliss traced an outbreak of scarlet fever to a carrier, and Stevens and Dochez (Jour. of Exp. Med., 1924), to an epidemic which was evidently milk-borne.

Dick and Dick succeeded in 1923 in producing experimental scarlet fever in a percentage of human beings. The same observers were able to show that filtrate from broth cultures of streptococci (scarlatinæ) contained a toxin, and that this toxin,

when used intradermally for diagnostic purposes, produced a reaction similar to that seen in the Schick test in susceptible human beings. This toxin is neutralized by convalescent sera or sera of animals which have been immunized with the filtrate (toxin). Human beings can likewise be immunized.

Zingher's (Jour. Amer. Med. Assoc., Aug. 9, 1924) studies confirmed those of Dick and Dick. He demonstrated that in the early stages of scarlet fever a reaction occurs with the toxin (broth filtrate), but as the disease progresses and the patient develops immunity the reactions become negative.

We take the liberty of quoting the conclusions of Dochez (Medicine, Aug., 1925) at length because his summary gives us a complete review of the scarlet fever situation:

"Have we now reached the end of man's long struggle to find the cause of this interesting and at times formidable and dangerous disease? Personally, I think we have. Belief that scarlet fever may be caused by a protozoan parasite, or by one of the mysterious ultramicroscopic viruses, must, I think, be discarded in view of the fact that the evidence brought forward in support of the causative relationship of such types of micro-organisms to the disease is entirely unconvincing. On the other hand, can we say with certainty that scarlet fever is caused by a type of *Streptococcus hemolyticus*? Certainly a chain of evidence in favor of this organism has been patiently and progressively forged which is as strong as that in many diseases whose etiology is now accepted without discussion. The constant association of this organism with the primary and

secondary manifestations of the disease, its specific character, its capacity to produce the experimental disease in man and in animals, the quality of human convalescent scarlet fever serum to neutralize the toxic effects of this streptococcus, the capacity of an antistreptococcus horse serum antitoxic in nature to counteract the specific toxic manifestations of the disease in man, and finally the isolation from Berkefeld filtrates of this streptococcus of a toxic substance which bears a specific relationship to immunity in scarlet fever, leaves little room to doubt that *Streptococcus scarlatinae* is the principal and probably only etiological agent of scarlet fever."

**Rheumatism.**—Rheumatism may be divided into various types. The infectious type in which we are interested may be divided into 2 series, the acute and the chronic. Poynton and Paine, Walker and Beaton, and Beatty all agree in finding the streptococci in the acute form of the disease. In the chronic form investigators generally announce the presence of a streptococcus.

Frequent attention has been called to the association of rheumatic conditions with diseases of the throat. Senator has emphasized the significance of nasal conditions in rheumatism. He considers acute articular rheumatism a subpyemia. The pyemiform picture represented by acute articular rheumatism suggests to him merely a lowered resistance to infection and not an absolute abolition of the same. Operations on the nose and acute infections lowering the vitality of the mucous membrane seem to afford ideal conditions for bacterial invasions into the general system, while the lymphatic system

of that region is especially favorable for the conveyance of bacteria.

Billings made a careful study of chronic focal infections and their etiological relations to rheumatism, nephritis, etc. The site of the focal infection may be the faucial tonsils, the peritonsillar tissues, supratonsillar fossæ, the lymphoid tissues, or membranes of the pharyngeal spaces. Abscesses of the gums and alveolar sepsis, pleuritic and pneumonic lesions, and chronic ulcers of the intestinal tract are also considered frequent sources. The genitourinary tract or gall-bladder may often be the original site of the trouble.

In 1900 Poynton and Paine isolated a diplococcus from the infected joints and from throats of patients suffering with the disease. Popoff obtained cultures of a micrococcus from the blood of rheumatic-fever patients. Achalme described an organism resembling the anthrax bacillus which he isolated from recent cases of rheumatic fever. He could not reproduce the disease in animals. Thirollox described an identical bacillus and reproduced lesions in rabbits. Achalme's bacillus has frequently been found by other investigators and is often associated with the diplococcus. Dana, Westphal, Wassermann, and Malkoff all reported finding a diplococcus.

Beaton and Walker (Brit. Med. Jour., Jan. 31, 1903) isolated a "*Micrococcus rheumaticus*." This *Streptococcus rheumaticus*, as it has been generally called in this country, exhibits no distinct characteristics. It is a small diplococcus growing in chains; has strong acid-forming properties, fermenting dextrose, levulose, galactose, maltose, arabinose, dextrin, saccharose, lactose, salicin, and mannite. It does

not ferment inulin, dulcitol, or sorbitol. It turns milk acid, but does not, as a rule, form a clot. It forms acid in bile-salt-lactose-broth, precipitating the albumin and bile salts. It is said that, if the broth in which the *Streptococcus rheumaticus* has been grown is filtered, other forms of streptococci will grow well in the filtrate, whereas the same organism will not.

F. M. Wood (Chicago Med. Recorder, Apr., 1917) has recommended an autogenous vaccine made from diplococcus rheumaticus, obtained from the oral cavity. If it is impossible to secure an autogenous culture one should begin with a stock vaccine and try to secure the culture later. In the various forms of chronic rheumatism, or arthritis, while the cause may not be primarily bacterial, there is often a secondary infection and much good will come from the use of a stock vaccine made from mouth organisms or from those secured from any focus of infection discoverable. If the first vaccine used does not succeed, another should be tried, and so on until a satisfactory one is found, or the possibilities are exhausted.

It is probable that in rheumatic conditions and complications such as nephritis, endocarditis, etc., there are often mixed infections or secondary infections to be considered. D. J. Davis gave this subject careful consideration in 28 cases of arthritis. Hemolytic streptococci were obtained from the tonsils in all cases and were predominant in most of them. In many the growths were practically pure. In 2 pneumococci were found, and in another the *Streptococcus mucosus* (pneumococcus Type III) occurred in conjunction with a few hemolytic streptococci. The joint fluids and blood were invariably sterile.

**Rheumatoid Arthritis.**—Lyon Smith had favorable results in the treatment of this condition. Five cases reported. He believes the *Diplococcus rheumaticus* has considerable claim to be considered as of etiological importance in rheumatism. Wolverton, Ball, Bannatyne and Lindsay have likewise witnessed satisfactory results.

Twenty cases of chronic arthritis of various types, all tentatively diagnosed as due to streptococcal infection and treated with streptococcus vaccines, have been reported by Jones. The results in at least 8 cases indicated that streptococcal infection is concerned in chronic arthritis, though fluid removed by puncture and blood-cultures was sterile. The vaccines used were of streptococci obtained either from the mouth (in cases of oral sepsis), from the urine, or from the feces.

J. H. Richards (Jour. of Bacter., Sept., 1920) reported on blood cultures from 104 cases of arthritis. *Streptococcus viridans* was found in 14 cases. Joint cultures were made in 54 cases, of which 4 were positive. Chronic endocarditis was found in 11 cases. There was a history of acute rheumatic fever in 12 cases, and of chorea in 2 cases. Foci of *Streptococcus viridans* infection were found as follows:

Teeth .....	50 cases
Tonsil .....	40 cases
Sinus .....	11 cases
Prostate .....	2 cases
Pyelitis .....	1 case
Salpingitis .....	1 case

Complement fixation with *Streptococcus viridans* antigen was positive in 68 cases.

As stated by Rolleston (Brit. Med. Jour., Oct. 3, 1925), the infection is



obviously of low virulence and of a very chronic nature. Various streptococci are most frequently incriminated. The treatment is primarily preventive—hygiene of the mouth and other sites of infection. Removal of infected teeth, tonsils, and adenoids and other foci is necessary, but he cautions against curetting an infected uterus. Autogenous, not stock, vaccines should be employed. When more than one organism is suspected, a monovalent vaccine may be tried, but a mixed vaccine may be necessary. This treatment may be combined with diathermy, ultra-violet radiation and diet. Non-specific proteins are also suggested, such as peptone, milk and T. A. B. (triple typhoid) vaccine. Ackland (*loc. cit.*) condemns all crowns, bridges and dead teeth, whether the skiagram shows mischief or not. Vaccines for pyorrhea are useless, in his experience, but as a part of the treatment after extraction a vaccine is most useful. Willcox (*loc. cit.*) states that vaccine therapy should never be used until the focus of infection has been removed, as far as is possible. Autogenous vaccines made from the organism believed to be causing the toxemia are isolated from the infected teeth or other primary focus or from the colon washings. It is very important that overdosage be avoided, it being best to give an initial dose of 2 minims of a vaccine containing 5 million per cubic centimeter and gradually increase the dose.

#### GONOCOCCUS.

The gonococcus is responsible for infections of various mucous and serous membranes; it may cause septicemia and endocarditis. The most common clinical manifestations of gonococcal infection are acute and chronic anterior

and posterior urethritis, prostatitis, orchitis, and inflammation of other structures intimately connected with the urethra—cystitis, Cowperitis, seminal vesiculitis. In the female it is a frequent cause of vulvovaginitis, endometritis, and salpingitis. It is also the cause of serious and rapidly developing ophthalmia, especially of the newborn. Among the metastatic infections caused by this organism are gonorrheal arthritis and less frequently iritis.

To the vaccine therapist the gonococcus is particularly interesting on account of its location in the tissues and its relation to the lymph supply of the infected part. In the beginning of their activities the cocci grow in the superficial epithelial cells, but soon penetrate between the cells to the deeper layers, where they continue their irritation as the superficial cells desquamate. This fact may explain some of the failures reported to have followed the use of vaccines. There has been a tendency on the part of some genitourinary surgeons to administer enormous doses of gonococcus vaccine in the treatment of **acute urethritis**—as much as 10 billion at a single dose. Such doses, if not harmful in any way, would evidently be advantageous in bringing about sufficient local hyperemia to overcome the effort of the organisms to protect themselves from the body fluids. On the other hand, Lespinasse gives very small doses. He says that in acute cases very few favorable results have been reported, but as the disease becomes more chronic the results of vaccine therapy become progressively better. The same thing applies to acute and chronic complications. The dosage is believed to be very important and should be accurately adapted to each patient. In acute cases,

doses as low as a million, repeated every day, have been given with fair results. In less acute cases 5 to 10 million are given at the start. This amount is increased from 1 to 5 million at each dose, giving the doses every five to seven days. In **chronic urethritis** the initial dose is 20 million, and this amount is increased 5 to 10 million, each time giving the injections about one week apart. Lespinasse lays stress on mixed infections and favors a mixed vaccine.

H. Culver (Jour. Amer. Med. Assoc., Feb. 3, 1917) compared 3 vaccines: *Gonococcus* vaccine, 100 million killed organisms; *meningococcus* vaccine in the same dose, and *colon bacillus* vaccine, 25 million. The results were identical. Intravenous injection was followed after 20 minutes to 1 hour by a chill, with or without headache and nausea or vomiting, severe pain in the affected part, a slight fall of temperature followed by a slow rise to a maximum in from 1 to 4 hours. The temperature then fell to normal in 24 hours. No benefit was observed when the dose was insufficient to provoke the typical reaction.

Boeckel and Bilger (Rev. de chir., Sept., 1923) have had favorable results in **gonorrhea** with a stock vaccine prepared at the Institut Pasteur, Paris. This vaccine is a saline suspension of 4 strains of gonococci—2 from acute urethritis, 1 from fatal gonococcal sepsis and 1 from peritonitis following salpingitis. It contains 1,000,000,000 bacteria per cubic centimeter. In a first series of 6 injections, 0.25 to 1 c.c. is injected subcutaneously on alternate days. After an interval of four or five days another series of 6 injections of 1 to 2 c.c. doses is given. In acute gonorrhea a few cures were

obtained. In 23 cases of subacute or chronic gonorrhea its use after failure of irrigation treatment yielded 12 cures, 3 partial successes and 8 failures. Complete cure usually required 28 to 30 days, in a few instances much less. The vaccine is asserted to have protective power against joint and other complications, or greatly to diminish their severity.

In 63 cases treated with autogenous vaccines by the same authors, complete cures were obtained in 86.2 per cent. They consider a combination of autogenous vaccines and local measures very useful in chronic gonorrhea. Gonococcal vaccines are indicated in these cases when local treatment has failed and the gonococcus is present. Non-gonococcal autogenous vaccines are of importance in secondary chronic infection. Autogenous vaccines are contraindicated in acute gonorrhea, in which the stock vaccine and local measures are generally effective. Where gonococci are not found in the urethral discharge, the autogenous vaccine is made from the seminal fluid. Colonies of gonococci and associated bacteria are mixed in 10 per cent. Lugol's solution and heated to 60° C. for 20 minutes. The vaccine contains 1 to 4 billion gonococci and 5 to 20 billion associated germs per cubic centimeter. The injections are made into the gluteal muscles in series of 6 to 10 at intervals of two or three days, in progressively increasing dosage. Intervals of 12 to 15 days are allowed between series.

According to Ravogli, vaccine therapy for gonorrheal affections has a value—not absolute, but relative to its localization and complications. Alone it is not capable of extinguishing the

process in the urethra, but it may shorten the process if combined with local antigonorrheal measures. It seems more active in secondary gonorrheal localizations. The injections given under the skin or in the muscular masses cause no inconvenience, but the reaction is generally accompanied by fever.

Extensive researches on the removal of the endotoxins from the gonococcus and other organisms were undertaken by Thomson (Lancet, Mar. 8, 1919) to produce non-toxic vaccines which could be injected in sufficiently large doses to develop a great amount of immunity. The toxicity of most germs was successfully reduced some 50 to 100 times. The gonococci, when detoxicated, could be administered in acute cases in doses of 2500 millions and increased to 10,000 millions. These large doses caused even less toxic symptoms than the small doses of the ordinary vaccine.

The therapeutic results obtained corresponded very markedly with the serologic tests. Thus it was found that the cases which showed the highest degree of immunity as estimated by the complement-fixation test recovered much more rapidly, and *vice versa*.

Lees (Lancet, June 28, 1919) likewise used detoxicated vaccine. The outstanding result was the rapid disappearance of purulent discharge and gonococci. Complications after commencing treatment were entirely absent; marked infection with secondary organisms was rare, and the patient's general health was improved. Clinical and serological results were parallel.

#### Differential Diagnostic Reaction.

—Irons has called attention to the value of the reaction following the injection of gonococcus vaccine as a

diagnostic point. He says: "A typical gonococcus reaction is characterized by a rise in temperature, often only slight; an increase in pain and tenderness in the affected joints, with occasionally some increase in swelling, and a variable degree of malaise. The symptoms follow the injection in from eight to twelve hours, and commonly last about twenty-four hours. Frequently there is a decided tenderness at the site of the injection, greater than occurs after the inoculation of the same dose of the same preparation in normal subjects. Occasionally there is a marked redness and edema lasting from twenty-four to forty-eight hours. There is usually a slight increase in leukocytosis in the first twenty-four hours after injection.

"The frequency with which these clinical phenomena occurred suggested the possibility of utilizing the reaction in the diagnosis of obscure cases of arthritis in which the gonococcus was the suspected cause."

Eight adults having no history or sign of gonococcic infection, and also a number of non-gonococcic cases, were given injections of 500 million dead gonococci. In none did a typical reaction occur. In a number of suspected gonococcus cases the reaction proved of value in making an early diagnosis. Among the cases adduced was one of monarticular arthritis with effusion in the knee, in which gonorrheal infection was denied. The patient was given an injection of 500 million. The temperature rose and the joint pains increased. The gonococcus was isolated in pure culture from the joint fluid.

Another patient, with aortic aneurism, who denied gonorrheal infec-

tion, had been selected for control by experimental inoculations. After an injection of 500 million cocci, the temperature, which had been uniformly normal, rose to 100° F. without any other apparent cause, returning to normal the next day. The prostatic secretion contained numbers of leucocytes with typical intracellular gonococci.

Herald (Jour. Amer. Med. Assoc., Jan. 31, 1925) has reported some experiments with filtrates of broth culture of gonococcus which he claims gave a positive skin reaction (when used intradermally) in dilution of 1:100 in infected individuals. He used Torrey strain No. 34. Further work may confirm that these findings with intradermal tests may be of service in the diagnosis of conjunctivitis, iritis, keratitis, etc., where it is impossible to obtain a history and evidence of existing infection.

Vaccine alone is insufficient to control or cure gonorrhea in the original sites of infection, such as the urethra, vagina, and conjunctiva, according to Cappelli, but is of help in what may be called secondary localizations of the gonococci, such as **epididymitis** and **arthritis**.

Hitchens and Brown (Amer. Jour. Pub. Health, iii, No. 9) reported a study of 46 cases of chronic **prostatitis**. They obtained gonococcus by culture in 5 cases, staphylococcus aureus in 11, staphylococcus albus in 24, non-liquefying cocci in 34, streptococci in 27, diphtheroid bacilli in 31, and colon bacillus in 2.

MacKinney carefully studied the effect of vaccines in 86 cases of gonorrhea and its complications. He stated that small doses of from 5 to 50 million rarely cause any local or constitutional

disturbance, and only with the dose increased to from 300 to 500 million was any disturbance noticed.

In all, 424 injections were given. The results are summarized with the statement that bacterial vaccines have not demonstrated their value in the treatment of acute or chronic gonorrhea or in the treatment of its acute complications. In metastatic infections, gonorrheal arthritis, they have given good results in a few cases.

Shropshire treated a large series of cases, including practically all the forms of gonococcal infection. The total failures in 500 cases amounted to only 6.7 per cent. It was never necessary to give more than 150 to 200 million gonococci at a single dose.

According to Buka, in both the acute and chronic forms of gonorrhea there is marked lessening of the danger of complications. The annoying factor of long-standing gleet was so satisfactorily overcome with vaccines that their use is invariably advocated when such a sequel occurs.

Lumb treated 500 consecutive cases of acute gonorrhea with vaccines. The general effects were: 1. Mental relief at the rapid disappearance of the discharge. 2. Rapid disappearance of pain on micturition. 3. Rapid disappearance of pain on irrigation. 4. Exercise could be taken without delaying the cure. Of the 500 cases 222, or 44 per cent., had some form of complication. The average duration of the 278 uncomplicated cases was 35 days, or 5 weeks. The average stay of all complicated cases was 52 days. It has from time to time been suggested, though never with adequate proof, that vaccines are dangerous in the acute stage, and lead to complications. This was not the case. Of

the 101 epididymitis cases, 70 had been present on admission, leaving 31 developed out of 430 cases, or 7 per cent. Of the 10 arthritis cases, 8 had been present on admission, leaving 2 developed out of 490 cases, or less than 1 per cent. The most remarkable feature of all was the exceptionally low percentage of relapses—less than 1 per cent.

**Urethritis.**—Read treated 6 cases of **acute gonorrhea** with autogenous and stock vaccine. The doses ranged from 10 to 100 million at three- to five-day intervals. In no case were the vaccines of benefit. The vaccine seemed to be of positive benefit, however, in 1 case of **Cowperitis** after incision and evacuation of pus. Seven chronic cases treated had been under observation for a year or more. In 5 of these, which had resisted all treatment for many months, the employment of vaccines in conjunction with some measures which had been used unsuccessfully formerly was followed by the disappearance of the disease within twelve to twenty weeks.

Palmer has had favorable results from stock vaccines in about 50 cases of **acute gonorrhea**. He advocates giving 2 minims of a 50 million vaccine with an interval of seven days. The doses are not increased except in occasional cases.

According to Livermore, good results are obtainable only in the complications of acute or chronic gonorrhea, which sometimes yielded promptly and satisfactorily to the administration of vaccine. The complications in which the vaccine gave the best results in his hands were **epididymo-orchitis**, **arthritis**, and **prostatitis**.

Cappelli reported 84 cases of **acute and subacute gonorrheal urethritis**

treated solely by vaccines, with 64 cures, or 76 per cent.; 32 cases of **chronic urethritis**, with 31 cures; 27 cases of **epididymitis**, with 26 cures; and 5 cases of **gonorrheal rheumatism**, all cured. Failures are attributed to the fact that a vaccine is not stable in composition. Complete rest in bed is emphasized.

**Mixed Infections.**—In the treatment of **chronic urethritis** and **prostatitis** it must be remembered that mixed infections are the rule. The chief rôle of the gonococcus seems to be to make the soil suitable for the growth of other bacteria. The other bacteria commonly found are streptococci, staphylococci, colon bacilli, and diphtheroids. A mixed vaccine should be used when the condition is of more than a few weeks' standing.

Buka reported a case of chronic urethral discharge which microscopic examination demonstrated was due to mixed gonococcic and streptococcic infection. The case presented a long prepuce, which called for circumcision. After the seventh injection of gonococcic and streptococcic vaccine the discharge completely disappeared. A week after the eighth and last dose, the prepuce was circumcised and the wound healed by primary intention. No complications developed, and recovery was considered complete.

Rush reported a case of chronic gonorrhea in which there was a history of several attacks of acute gonorrhea, one of these attacks having been accompanied by prostatitis and epididymitis. For ten days prior to coming under treatment he had profuse urethral discharge, burning sensation on micturition, pain in left testicle, and pain in elbows, ankles,

and wrists. Microscopic examination showed mixed infection of gonococci and staphylococci in the urine. Gonococci were found in the thickish brown pus from the urethra. Injections of 50 million stock gonococcic and 100 million stock staphylococcic vaccines were given for a period of three months, in conjunction with other treatment. Rush says: "The patient has gained in weight, feels better than in five years, has no rheumatic pains and no morning drop, nor shreds in urine." The case was discharged as cured at the end of the third month of treatment, and two thorough examinations proved negative.

**Epididymitis.**—Friedländer and Reiter treated 125 cases of acute, subacute, and chronic gonorrheal epididymitis with polyvalent vaccines according to Wright's directions. No marked systemic disturbances were noted—occasionally some restlessness, slight perspiration, and a little headache. The injections themselves caused no pain, but from twelve to eighteen or twenty-four hours after injection the affected organ became acutely red, the skin shiny, and there was a slight increase in the painfulness and swelling of the inflamed area. The authors considered these findings as a "local vaccination." This they consider especially important. Within several days resorption of the infiltration occurred. They concluded that vaccine treatment gives exceptionally good results in acute epididymitis and satisfactory results in subacute gonorrheal follicular prostatitis, in which case the course of disease is at least always shortened.

Many cases of chronic gonorrhea and complications seemed benefited, in

Sézary's (Prog. méd., May 14, 1921) experience, by an autogenous vaccine of staphylococci and other germs obtained from secretion after prostatic massage, mixed with a stock polyvalent gonococcus vaccine. Each cubic centimeter included 1 billion gonococci and  $\frac{1}{2}$  billion each of two other organisms, and the dose was 0.2 c.c., quickly increased every five to seven days. The injections were made intramuscularly. A febrile movement and focal activation, marked by increase of discharge, seemed prerequisite to benefit. With prostatic massage, the treatment gradually checked the discharge.

**Gonococcic Arthritis.**—According to Murrell, "The popular term 'gonorrheal rheumatism' has been gradually superseded by 'gonorrheal arthritis,' or, to be more precise, by 'gonococcic arthritis.' 'Urethral arthritis' has been suggested, but has met with little favor. All these names are open to objection, chiefly on the grounds that the arthritis is commonly a synovitis, and that in the chronic forms the organism is not the gonococcus but some later development in the bacterial world."

He concludes: "The ordinary stock gonococcic vaccine is of very little value. Somewhat better results are obtained by vaccine prepared from a recent alien gonococcic urethritis, but even that leaves much to be desired.

"I am in accord with Hartwell, who finds that autogenous vaccines are valuable in all stages of gonococcic arthritis except when ankylosis has occurred. I have treated many cases with alien vaccines, the doses of the injections being gradually increased from 5 to 200 million. In some cases I have used large doses, even up to 500 million, every three or four days. It is

said that the dose for the urethritis should be 75 million, for the iritis 250 million, and for the arthritis 500 million, but I do not endorse the action of the medical man who gave an initial dose of 825 million. The number of injections given ranged from 8 to 25, but in a chronic case this is inadequate. In a case of gonococcic arthritis of four months' duration treated with an autovaccine, the organism being a diphtheroid bacillus obtained from the urethra, the first injection of 5 million was given on June 1st and was gradually increased to 50 million. By the end of July, 20 injections had been given and the condition was cured."

Chronic gonorrheal arthritis is due, according to Hughes, to a mixed infection with the gonococcus and staphylococcus, both of which can be cultivated from the interior of the urethra. An autogenous vaccine containing from 100,000,000 gonococci and 150,000,000 staphylococci up to 500,000,000 of the former and 1,000,000,000 of the latter, should be used, and after the second dose the chronic gleet treated locally. Hughes had very good results with this treatment, though a complete cure often required weeks or months.

In 7 out of 10 cases of joint and tendon-sheath infection treated by Read, the results were direct and positive. He concluded that stock vaccines are seemingly as efficient as autogenous vaccines, but when these fail autogenous should be tried. Vaccines in acute gonorrhea are of no value. In one subacute case they were seemingly of benefit. In obstinate chronic cases they are of use in conjunction with other measures. In gonorrheal rheumatic conditions they are of positive worth.

Hartwell reviewed 51 cases of gonorrheal arthritis treated with gonococcus vaccines in the Massachusetts General Hospital. Vaccines killed by heating to 60° C. for one hour were compared with vaccines prepared without the use of heat. No striking differences were noted. The patients with acute conditions were inoculated more frequently and received smaller amounts than the more chronic ones. They received doses ranging from 10 to 25 million and progression was made up to 100 million. The doses were given at intervals of from two to four days in the acute cases, and every five days to a week in the more chronic ones. In the chronic conditions the amount was often pushed up to 500 to 600 million. Thirty-one, or more than half, the cases were seen when the acute inflammation had subsided. The joints were swollen, stiff, and painful when used. In 27 of these cases the result of treatment was successful and the patients were discharged with complete functioning joints without disability. In 9 of the acute cases the process in the joints had become purulent or seropurulent, with infiltration of the periarticular structures; 6 of these recovered with joints which were capable of complete free motion.

In arthritis the initial dose advised by Livermore is usually 50 million, with an increase of 50 million each time. Gratifying results were obtained. In the treatment of gonorrhea in women he has several times noted cases that seemed to be benefited by the vaccine. In his experience gonococcus vaccine has not proven a prophylactic against the occurrence of complications.

Eyre and Stewart state that "the

effect of vaccines was practically identical in all cases. In from twelve to twenty-four hours after the administration of 5 to 10 million the affected joints were subjectively more painful, and in many cases distinctly more swollen, red, and tender, and movements more limited. These symptoms correspond with the negative phase. In from thirty-six to forty-eight hours symptoms cleared up, pain and tenderness passed off, and movements became much more free." Some of their cases were treated with stock vaccines and some with autogenous preparations.

Maini found that in doses of less than 1 million the vaccine was ineffective, but that when given in this dose it caused a marked decrease in the painfulness of the joints, after a temporary increase for a few hours.

In 443 cases of gonorrheal arthritis Chiari applied vaccine therapy with autogenous or commercial vaccine. Only 41 cases were uninfluenced; 32 patients were improved and 367 cured.

In 15 cases of gonorrheal rheumatism, bedridden for months and unresponsive to treatment, Fraser and Duncan (Lancet, Jan. 31, 1920) injected vaccine intravenously. The largest dose of gonococci used was 2000 million. The vaccines used were not freshly prepared. As a result of storing, probably the toxins contained had broken down somewhat. The injection of these, possibly, non-specific germ constituents would seem to have caused the production of specific antibodies. There was marked improvement in all cases, without any appearance of a clinical negative phase. No benefit seemed to result from an injection that was not followed by pyrexia.

**Pyosalpinx.**—Some gratifying results have been obtained by Palmer in gonorrheal pyosalpinx, both in acute cases and in acute exacerbations. Four patients were treated, but since all of them were satisfied with the improvement they made and withdrew from further treatment before all signs of the disease were gone the results could only be recorded as symptomatic cures. Even this was gratifying, as all of them would have required hysterectomy if vaccines had not been used. The doses given one of these patients were 4 minims of the vaccine (1 c.c. = 50 million) administered every other day for a week and then twice a week. At the time she refused further treatment the tubes were too small, hard strings; leucorrhea was slight, and showed no gonococci. Favorable results were also obtained in 2 cases of gonorrheal rheumatism and in 1 of gonorrheal conjunctivitis.

**Vulvovaginitis.**—Among the earliest reports of work done in this country with gonococcus vaccine was that by Butler and Long (Jour. Amer. Med. Assoc., Mar. 7, 1908). These authors stated that they varied the dosage in different cases, being guided by the immunizing response. Inoculations were usually repeated every five or six days. Butler, in a later report, stated that the best results had been found to be obtained with doses of from 5 to 50 million.

Their first report covered 12 cases. In 4 of these the clinical appearance of gonorrhea disappeared in ten to twenty-one days; in 5 cases a longer period of treatment was required, and in 3 particularly stubborn cases the discharge finally ceased. The second report covered 25 cases—12 acute



and 13 chronic. Seventy-five per cent. of the acute recovered and the other 25 per cent. showed improvement; 85 per cent. of the chronic cases recovered.

Hess (Amer. Jour. Dis. of Child., Nov., 1916) urged that the cervix is usually involved, and that in chronic cases the vagina may show no signs of inflammation. Numerous pus cells without bacteria in smears made from the cervix indicate almost invariably a gonorrheal infection. In the newborn, however, the invasion of the vagina by saprophytic bacteria may cause a purulent discharge which is hardly pathologic. Gonorrheal vaginitis or cervicitis is not to be regarded as an institutional disease, as it occurs in a considerable proportion of infants living in crowded tenements.

In child-caring institutions the greatest obstacle to controlling the disease is the difficulty of recognizing latent cases. By means of provocative inoculations of gonococcus vaccine in doses of 100 to 400 million, Hess was able to convert the **concealed carrier** into an open case, and thus discover many which had escaped detection. Vaccinations have also some prophylactic value.

Alice Hamilton recorded 7 chronic cases in which local treatment had been given a fair trial, and failed to bring about improvement. While one case proved refractory, the other 6 improved decidedly under the injections of killed gonococci. While the average duration of vaginal discharge prior to treatment was nearly four months, the average duration after treatment was not quite three weeks. It was not claimed that a permanent cure had been effected in any of these children.

In a case of gonorrheal **proctitis** of 18 years' standing, with a tumblerful of pus voided from the rectum daily, Gautier and Jaubert (Bull. Soc. franç. d'urol., No. 7, 1924) witnessed an excellent result from treatment consisting solely of injections of an iodized autogenous vaccine, 13 doses of 2 to 6 billions of gonococci being injected at intervals of 3 or 4 days. After these injections there remained only a slight discharge appearing when the patient was fatigued, and several bacteriologic examinations, the last of which was made seven months after termination of the treatment, gave negative results.

**Conjunctivitis.**—Ohlmacher treated 3 cases of gonorrheal conjunctivitis, of which two were cured and one improved. Miller had favorable results in the treatment of two cases. Eyre has warned that unless the vaccine is given with extreme care and the injections are controlled by the opsonic index definite harm may ensue. He mentions a case treated with gonococcus vaccine in which an injection was given at the wrong time. Practically the whole cornea was lost.

According to Bryan vaccine is of great value in acute gonococcal conjunctivitis. Of 2 severe cases treated, in 1 a cure was obtained in ten days; in the other no apparent benefit resulted. He also treated 3 cases of gonococcal ophthalmia in newborn infants with doses of  $\frac{1}{2}$  to 1 million of vaccine; the disease was cured in each case without infection of the cornea.

Weeks has recommended doses of  $2\frac{1}{2}$  to 50 million of polyvalent gonococcus vaccine, but found it of little value in acute infection.

**Iritis.**—Eyre and Stewart reported on 4 cases of gonorrheal iritis, giving detailed accounts.

Case I.—The patient had suffered from gleet for ten months in this, his third attack of gonorrhea. Ten days after the second injection he said that the eye had been free from pain for a week for the first time for nearly six months. Treatment was carried out for two and a half months, at the expiration of which the iritis was cured and sight perfect.

Case II.—Present attack of gonorrhea contracted five months ago. Three recurrent attacks of conjunctivitis (both eyes), but no pain or loss of sight. Present attack, left eye only, starting one month previously; great pain, congestion, and loss of sight. Pain on admission very bad, and getting worse. Pain relieved within forty-eight hours of first injection; gone in four days; sight returning; eye steadily improving; patient feels better in general health two or three days after each injection. There had been no relief of pain prior to vaccine.

Case III.—Present attack of gonorrhea contracted one month before commencement of iritis. Lids injected and swollen, mucopurulent discharge, but gonococci absent; conjunctiva injected; chemosis; cornea healthy. Eleven days after admission, arthritis of knee and elbow. Arthritis well, and patient discharged cured in a month from first vaccine inoculation.

Case IV.—Patient admitted with "cold" in the right eye; marked conjunctival injection; discharge; very severe pain, especially at night; cornea cloudy; pupils dilated, iris dirty colored; condition getting worse. One month from date of admission,

eye greatly improved; no discharge; iris clear; no conjunctivitis; cornea clear. Pain relieved after first injection; cured after the second.

Reber and Lawrence recorded 3 cases of iritis in which the complement-fixation test established an old latent gonococcemia, and which yielded promptly to bacterin treatment.

**Accessory methods of treatment** are of much importance in gonococcus infections, and the usual methods of treatment are by no means contra-indicated when vaccines are used. As stated by MacGowan: "Vaccine treatment is to be added to the ordinary approved methods as an adjunct, but is not to be depended upon as a specific method of curing the disease in question."

#### STAPHYLOCOCCUS.

The staphylococci are the most common pyogenic organisms. It has been the tradition in textbooks from the early days to consider as pyogenic staphylococci the *Staphylococcus pyogenes aureus*, *Staphylococcus pyogenes albus*, and *Staphylococcus pyogenes citreus*. The *Staphylococcus pyogenes citreus*, however, is so rare that it scarcely ever need be considered as a producer of pus. The majority of those who have encountered organisms which would answer the description have been in considerable doubt as to whether it was not really either an aureus or one of the non-pyogenic cocci commonly found in water and in the air.

The pyogenic staphylococci may be isolated from the skin, frequently from the nose and throat, and from the feces of animals, and are ubiquitous in nature. In abscesses Allen found the staphylococcus alone in 67 out of 73 cases. One had streptococ-

cus alone and 5 a mixture of staphylococcus and streptococcus. Abscesses in various parts of the body, especially those superficially located, are practically always caused by the staphylococcus. It goes without saying that ulcers are either caused by the staphylococcus or are infected by it as a secondary invader. Ulcers are less frequently the result of a pure infection because there is every opportunity for other organisms to enter. Allen found a pure staphylococcus in only 16 out of 39 cases. A pure streptococcus infection was found in 5 and a mixture of staphylococci and streptococci in 18.

The *Staphylococcus albus* is the common organism associated with the acne bacillus, especially the pustular variety. *S. aureus* is found less often.

Diseases of the bone are usually caused by tubercle infections. When the condition is suppurative, however, the streptococcus is the most common associated organism. Ulcer of the endocardium, while more frequently the result of the growth of the streptococcus, may be caused by the staphylococcus. Septicemia, pleurisy, peritonitis, and meningitis may also sometimes be due to the pyogenic staphylococci.

Among the more chronic conditions caused by them may be mentioned syphilis.

From the preantiseptic days in surgery we have inherited the ability to make a diagnosis with a fair degree of accuracy from observation of the character of the pus. If it is of a creamy yellow color one may conclude that the *Staphylococcus pyogenes aureus* is the offending organism, or is one of the chief among the offenders if it is a mixed infection. Pus of a

whiter color, which used to be called "laudable pus," may contain *Staphylococcus aureus*, but probably contains the *Staphylococcus albus*.

Treatment of boils and carbuncles by staphylococcus vaccines has become a routine procedure. The literature contains a great number of reports and the results recorded have been uniformly good.

**Dosage.**—If the patient is very toxic or the disease extensive, the doses should be small (50 million) and repeated frequently, even as often as every day or every third or fourth day.

If the carbuncle is of only ordinary size and the patient is otherwise in good health, the doses may be much larger, from 250 million up to 1000 million.

The best plan is always to inject a small initial dose.

**Chronic furunculosis** is liable to recur, and for this reason it has been found advisable to continue injections of vaccine at intervals of two weeks to a month for about six months after all symptoms of the trouble have disappeared.

J. F. O'Malley (Lancet, July 18, 1925) states that in the recurrences which may take place in furunculosis despite every precaution, vaccine therapy promises the most effective line of attack. Autogenous vaccines are best, but if they are not obtainable stock vaccines are worth a trial. He observed excellent results from their use in some cases from such small dosage as 50, 100 and 200 million staphylococci (*pyogenes aureus*) in successive weekly doses.

In those patients suffering from an abscess which contains pus at a point very deep seated, it is a question for

consideration whether it is wise to attempt to abort such an abscess by the inoculation of small doses or attempt to induce a negative phase by a large dose, encouraging the abscess to break down. The question must be decided on clinical indications; if there is much pus present it will be absorbed only very slowly and a painful lesion will be present for a considerable period. If it is possible, good results are likely to follow the aspiration of the pus by means of an ordinary syringe. In staphylococcus infections a stock vaccine is nearly always successful.

Wright has repeatedly called attention to the value of sodium citrate compresses as an aid to the evacuation of the pus in order to bring a flow of fresh lymph to the focus of infection. The abscess is pricked with a sterile needle or with a small knife, and compresses soaked in a hot solution containing 1.5 per cent. sodium citrate and 5 per cent. sodium chloride are applied. The hypertonic solution tends to attract the fluids, and much of the broken-down tissue and infectious fluid will be found to come away on the gauze.

In the treatment of **ulcers** compresses containing sodium chloride and citrate are especially valuable. It is always advisable to have a bacteriological diagnosis made in the case of ulcers. They are more likely to be the result of mixed infections, as stated above, and if so a mixed vaccine should always be used. When it is impossible or not practical to have such a diagnosis made immediately, it is generally safer to conclude, for temporary treatment, that the staphylococcus and streptococcus are present and to use a vaccine containing these organisms.

The initial dose of the mixed vaccine may be estimated at 50 million staphylococci and 10 million streptococci.

**Sinuses** and **fistulas**, especially **fistula in ano**, are rendered more difficult to treat by reason of their peculiar pathology. The tract is the seat of infection throughout its whole course, and if it is at all chronic it is composed of a thick layer of granulation tissue, the so-called pyogenic membrane.

It is generally advisable to administer several doses of vaccine before removing this pyogenic membrane by surgical treatment.

**Staphylococcus Vaccine.**—Stoner (Maryland Med. Jour., May, 1911) has given some collective results obtained by the use of bacterial vaccines in a large number of staphylococcic conditions. These results summarized in the subjoined table.

Disease.	Number of cases.	Cured.	Improved.	Not benefited.
Cancrum oris ..	1	1		
Prostatitis .....	6	6		
Adenitis .....	3	2	.....	1
Salpingitis .....	2	2		
Acne .....	139	74	48	7
Carbuncles .....	24	23	1	
Furunculosis ....	140	125	12	3
Sycosis .....	28	13	10	4
Atrophic rhinitis.	10	.....	10	
Sinusitis .....	3	.....	3	
Otitis media ....	34	19	11	4
Local infections.	114	39	55	20
Postoperative infections .....	39	28	7	4
Totals	543	332	157	45*

\*Sic.

Carmalt Jones reports 120 cases treated with staphylococcus vaccine. The following table shows the results:—

Disease.	Number of cases.	Cured.	Improved.	Un-changed.
Abscess .....	96	67	23	6
Impetigo .....	10	4	4	2
Sycosis .....	8	3	4	1
Ulcer .....	3	.....	3	.....
Acne .....	2	.....	2	.....
Cystitis .....	1	.....	1	.....
Totals .....	120	74	37	9

MacGowan has reported the treatment of 2 cases of **chronic cystitis** with staphylococcus vaccine. In both small doses were used (80 million), the intervals between being only two days. In 1 case four such doses were necessary, and in the other only two, to clean up the general condition, reduce temperature, and relieve the septic state.

Gruca (Zent. f. Chir., July 26, 1924) used Delbet's vaccine in twelve cases of **furunculosis** of the face, 2 doses of 4 c.c. being injected. Complete recovery followed in five to twelve days, even in severe cases.

Beeman has treated successfully with bacterial vaccines a **chronic blood infection** caused by the *Staphylococcus aureus*.

During the preparation of the autogenous vaccine, which takes 2 days, H. Beattie Brown frequently gives an initial dose of a pure staphylococcus aureus or albus vaccine, prepared and kept on hand in the laboratory. If the offending organism corresponds to the organism of the vaccine used in the first treatment, and if there has been an improvement, the stock vaccine is continued.

Nagle has been interested specially in the treatment of **chronic suppurative ears** by vaccine therapy. The results were uniformly good. Out of

40 cases there was only 1 in which the vaccine failed to cure the discharge. The cause in this case was a staphylococcus. There was marked improvement in cases of **atrophic rhinitis** with crusts and odor. To keep these patients in the improved condition it appeared necessary to continue the treatment.

Thompson has given an interesting account of a case in which the use of staphylococcus vaccine was followed by remarkable results. The pathological condition was an infection of the forearm following a burn on the hand. **Septic pneumonia** developed, accompanied by suppuration of the wrist. In rapid succession appeared arthritis of the right knee-joint, pyonephrosis, and, finally, a spreading abscess which extended over the upper side of the chest wall and shoulder. The surgeons refusing to operate, treatment with bacterial vaccine was started and was immediately followed by such improvement that operation became possible and 12 ounces of pus were removed from the abscess on the shoulder. Four subcutaneous inoculations were given at weekly intervals, three of 100 million each and one of 200 million. Immediate drop in the temperature followed the first inoculation, and subsequent rises were controlled by further injections. In a month recovery was complete.

Sherwood treated successfully a case of true **staphylococcus pyemia**, following difficult labor with forcible dilatation of the cervix. The staphylococcus was isolated in pure culture. In spite of 8 injections of a mixed vaccine containing streptococci, staphylococci, and colon bacilli, there was no apparent benefit. An autogenous vaccine was made and its use

was followed by immediate change in the condition of the patient. The dose was 40 million dead bacteria, and immediately after the second injection given the next day, consisting of 60 million bacteria, there was immediate reduction in temperature to the normal point. Three subsequent injections, 1 of 60 million and 2 of 40 million, were made at intervals of several days.

Although Villandre and Rochaix (Ann. de méd., Jan.-Feb., 1918) found operative measures effectual in the treatment of 47 of the 61 cases of infectious complications following 450 war wounds of the skull, in 14 cases an inaccessible **abscess** developed in the **brain**. A cure was realized in 3 cases given autogenous vaccine treatment, although the abscess returned later in one of the cases. Nearly 50 per cent. died of the 11 not given vaccine therapy. The *Staphylococcus aureus* was cultivated almost constantly from the projectiles and scraps extracted from the skull wound, even in those that healed apparently aseptically.

Besredka having shown that filtered cultures of staphylococci may induce a high degree of immunity when applied to the skin in guinea-pigs, Bass, Soupault and Brouet (Presse méd., Jan. 16, 1924) tried such treatment in man, using filtered stock vaccines to which were added autogenous vaccines as soon as the latter were ready. The vaccine was either applied with compresses over large areas of the skin, or instilled in wounds or injected intradermally around them. The cases treated included **cellulitis**, extensive **lymphangitis**, abdominal and pleural **fistulas**, **osteomyelitic abscesses** and **sinuses**,

and suppurative **arthritis of the knee**. In all instances the local application is stated to have been followed by rapid subsidence of inflammation and healing of the affected tissues. In osteomyelitis with denuded bone, scraping and resection proved unnecessary. In a sluggish subphrenic pyopneumothorax the fistula closed in 11 days.

**Sycosis.**—Sycosis is one of the difficult diseases to treat with bacterial vaccines. It is a very chronic condition and results in diminished powers of resistance in the skin, while irritation is kept up by local conditions such as nasal discharge and dust. At the same time the bacteria are so located with relation to the lymph-supply that it is difficult for the better quality of lymph to reach them. For these reasons relapses are liable to occur. Results will be enhanced by methods assisting in overcoming such conditions, depilation by the X-rays or other means considerably aiding in the cure. But even this treatment may have to be prolonged.

**Periostitis and Osteomyelitis.**—When tuberculous bone disease is complicated by staphylococci, as in **psoas abscess**, vaccine treatment is of considerable assistance to the surgeon. The vaccine should contain all varieties of bacteria present in the pus and be used in conjunction with tuberculin.

**Prevention in Surgical Work.**—Vaccines have been found of benefit before operation, especially in regions likely to become infected or where it is a question of operating upon an infected site which may be partly or entirely walled off. Such conditions are mastoid operations, operations upon the nose, the tonsils, appendiceal abscesses,

pus tubes, sinuses and fistulas of various kinds, empyema, etc. The vaccine to be injected depends, of course, upon the type of infection. The doses used also depend upon the general condition of the patient and the location of the focus of infection. A few attempts have been made to prevent postoperative pneumonia by vaccines. About 500 million staphylococci and from 150 million to 250 million streptococci are injected about a week before the operation. It is also advisable that the vaccine contain colon bacilli. Apparently good results have been obtained.

#### COLON BACILLUS.

As the pneumococcus is almost constantly present in mixed infections above the diaphragm, so the colon bacillus and its near allies are especially associated with diseases below the diaphragm, either alone or in conjunction with other bacteria such as the staphylococcus, streptococcus, pneumococcus, *Micrococcus tetragenus*, and *Bacillus pyocyaneus*. In treating infections due to the colon bacillus, it must be remembered that there are many varieties of this organism and, according to the findings of Avery, vaccine of one type has no effect on a condition due to infection by another type.

Allen called attention to certain important facts in regard to the treatment of colon infections. These are:—

1. The fact that the term *Bacillus coli* is a generic one. Thus, Glenn pointed out that other organisms, such as *Bacillus cloacæ*, which very closely resemble the *Bacillus coli*, may produce cystitis. It is necessary to employ the autogenous vaccine whenever possible, and in default of this a highly polyvalent vaccine.

2. That not only is the vaccine, especially if heat be employed to secure sterility, highly toxic, but also that sinuses due to this organism show a marked tendency to close—a tendency which must carefully be counteracted, or rigors and other signs of auto-intoxication will ensue. Where this is likely to occur, an initial dose of 25 million should not be exceeded. Later, very much higher doses, even to 1 billion, may be safely employed.

3. It would appear that, after an autogenous vaccine has been employed for six to eight weeks, the living bacteria at the site of infection occasionally manifest the power of elaborating a protective substance. This difficulty may be surmounted by taking fresh cultures and preparing a new vaccine.

4. The discharge of bacilli in cases of *bacilluria* may be markedly intermittent. It is never safe, therefore, to assume that infection has disappeared because one or two examinations of the urine point in this direction. Such examinations must be repeated at intervals of about three days for at least as many weeks. In this connection it must be remembered that certain cases which appear to be merely cystitis are in reality ones of renal disease, and may be complicated by tuberculosis; while *bacilluria* may merely be evidence of colon infection elsewhere in the abdomen, as in the bowel, uterus, or old caseous abdominal glands.

If due regard be paid to these important points, it may be said that the prognosis is almost uniformly favorable in sinus cases, whether coming from the region of the liver and gall-bladder, appendix, pleura, or bone, provided, however, that the appropriate surgical measures can be also pursued.

Among conditions most amenable to vaccine treatment may be mentioned **peritonitis, cystitis, urethritis, pyelitis and pyelonephritis, endometritis, enteritis, appendicitis, cholecystitis, subphrenic and hepatic abscess, empyema, and suppurative periostitis.**

The colon bacillus and streptococcus vaccines have been recommended by W. W. Crawford (So. Med. Jour., June, 1912) in **acute appendicitis** in conjunction with operative treatment, *e.g.*, 50,000,000 dead colon bacilli on the first day, 100,000,000 on the second, 200,000,000 on the third, and 400,000,000 on the fourth. Many of his cases with tumor and fever either passed rapidly into the "cold" stage, where simple drainage, or drainage with appendicectomy, became possible, or, when suppuration was slight, convalesced without drainage. In acute perforative appendicitis, if operated upon early, liberal doses of vaccine are helpful unless the patient is already overwhelmed with toxins. A. C. Guthrie (Brit. Med. Jour., Jan. 9, 1915) employed anticolon-bacillus serum and vaccine in 22 cases, which recovered without operative measures. Most of the cases were acute. The best dosage was 20 c.c. (5 drams) of anticolon-bacillus serum, 10 c.c. (2½ drams) being injected subcutaneously first in the right and then the left hypochondriac region. A few days later 100 million colon-bacillus vaccine is injected in the deltoid region, to prevent recurrence. As other organisms may be causative, the "fixation of complement test" should be tried, using the patient's serum and the most probable organism (*B. coli*, pneumococcus, streptococcus). A corresponding serum or vaccine is then used. A striking re-

lief of pain and a feeling of well-being followed the serum injections.

Hugh Cabot has reported on the use of vaccine in the treatment of infections of the urinary tract with the exception of tuberculous and gonococcus infections. The report comprises chiefly those infections due to the colon bacillus and pyogenic cocci. Thirty cases were under observation; the colon bacillus was the infecting organism in 22; the colon bacillus mixed with the streptococcus or with the staphylococcus was found in 3. Treatment was continued for two months to two years, the average being slightly less than ten months. In 19 cases there was definite relief of symptoms, varying from marked improvement to complete *symptomatic cure*; in the remaining 11 cases there was no definite relief. In all cases a culture was obtained two months to two years after cessation of the treatment. Three remained free from bacteria; the remaining 27 all showed bacteria and were therefore not benefited as to the presence of bacteria.

Colon infections of the **prostate** which have resisted all ordinary treatments have, in a number of instances, been improved by vaccine (Irons).

Hartwell and Streeter treated 19 cases of urinary tract infections with bacterial vaccines. Nine were infections of the bladder alone, and 10 of the bladder and kidneys, including the ureters. Autogenous vaccines were used in all cases. They concluded that vaccines are efficient in relieving the symptoms in mild forms of cystitis, have a less marked effect on pyuria, and are without value in severe cystitis. They probably hasten recovery from pyelitis.



Hale White and Eyre reported excellent results from autogenous vaccine in a severe case of **cystitis** and double **pyelitis** accompanied by vomiting, high fever, and rapid pulse.

In non-surgical infection of the **kidneys** and **ureters**, G. J. Thomas advises a careful search for foci of infection such as tonsils, teeth, abscesses, furunculosis, bone infections, etc., before urologic treatment is instituted. In the local treatment, lavage of the renal pelvis and ureters every 4 or 5 days is most frequently used, with 0.5 to 3 per cent. silver nitrate. Autogenous vaccine and urinary antiseptics are also given. Of 150 cases, 46 per cent. were thus improved and 18 per cent. more cured.

Roger-Smith treated several cases of **colon bacilluria** with autogenous vaccine. One man of 40 had had 7 attacks of "influenza" in nine months. The urine was loaded with *B. coli*; colon bacilli persisted in spite of medicinal treatments and he had slight fever at times. After 12 injections of prepared vaccine in doses of 50 to 250 million the urine became sterile and all symptoms disappeared. In a man of 74 who had had a prostatectomy several years previously, intense bladder irritability and purulent discharge from which *B. coli* was cultivated cleared up under autogenous vaccine.

According to M. J. Synott, correct applications of *B. coli* vaccine by skillful hands in **acute bacillus coli pyelitis**, **cystitis**, **ureteritis**, and **nephritis**, with fever and other evidences of systemic infection have produced results ranging from a complete cure to considerable amelioration of the symptoms related to micturition, the local discomfort, pyrexia, anemia, and loss

of weight. The dose of the autogenous vaccine is 5 to 20 million every five to seven days.

Butler Harris called attention in 1908 to the treatment of **mucous colitis**, in which he had obtained good results. This was confirmed by others. The pain is lessened, the diarrhea, mucus, and blood diminished, and the general health much improved.

A. H. Drew (Jour. State Med., London, July, 1918) treated with great success 15 cases of **membranous colitis** by means of autogenous vaccines. The membrane in all cases swarmed with bacteria, of which the Gram-positive forms predominated. In fourteen of the cases the enterococcus was observed, together with *Streptococcus fecalis*. The writer found that many patients are extremely susceptible to the enterococcus, hence initial doses of vaccine of not more than 2 to 3 million cocci should be given. The treatment should be continued with gradually increasing doses till 500 million cocci can be injected without producing reaction.

J. A. Bargaen and A. H. Logan (Arch. of Int. Med., Dec., 1925) report having obtained a Gram-positive diplococcus in pure culture from the early lesions in an acute exacerbation of cases of **chronic ulcerative colitis**. By intravenous injection of the organisms, lesions like those in human beings were produced in rabbits and dogs. For treatment a killed suspension of these organisms was found of value. The sterile filtrates of 24-hour cultures in 1 per cent. dextrose broth were also used.

Bonny has emphasized the great frequency and the gravity of the presence of *Bacillus coli* either alone or with other organisms in **puerperal sepsis**. Care should be taken to dis-

criminate between a case of *true* puerperal sepsis and one of a *localized infection* of the uterus by the colon bacillus. Should blood-cultures confirm the bacteriological findings in the uterine discharge one should not hesitate to have immediate recourse to vaccine therapy. The worse the condition of the patient, the greater the necessity for prompt action. Everything depends upon the reserve strength of the patient. If this is adequate to tide the patient over for two or three days, an autogenous vaccine should be used in doses from 5 to 10 million. In twelve to eighteen hours the temperature should drop from 2° to 3° F.; the pulse and general condition should improve. Any sharp rise or a steady rise continued over twelve hours calls for a fresh injection.

Wright and Reid treated 2 cases of **cholecystitis**, both of which were cured. The first case was one of obstructive jaundice which had not been relieved by operation. The colon bacillus was isolated from the bile and an autogenous vaccine made. Three injections sufficed to obtain a cure. The second case was one in which fourteen stones had been removed two months previously. The wound would not heal and the patient's condition was generally poor. Vaccine treatment produced a slow but complete recovery.

Turton and Parkin treated a patient whose gall-bladder was found distended and contained a large stone. From the secretions *Bacillus coli* was isolated. Because of his slow progress an autogenous vaccine was prepared and, after three injections of 500 million each, rapid and complete recovery resulted.

As regards the use of vaccines in **pre- and postoperative infections**, L. J. Hammond (Atlantic Med. Jour.,

Dec., 1924) has reported having used vaccines with some success in acute cases of colon bacillus infection in doses of 2 million to 1 billion, eight doses being given at five-day intervals. In subacute and chronic staphylococcus infections, the dose ranged from 25 million to 1 billion, with preference given to an autogenous vaccine when a pure culture could be obtained.

#### **MENINGOCOCCUS.**

Aside from the use of antimeningococcus serum, a vaccine standardized by Wright's method and prepared by the suspension of killed meningococci in normal saline solution has also been used for prophylaxis.

Such a vaccine has likewise been used therapeutically in a few cases. Emery reported its use in 4 cases with 3 recoveries and 1 death, and expressed the belief that the vaccine is well worthy of a trial. The most striking thing about the injections was the clinical improvement which followed almost every dose. The initial dose was 250 million; the following doses were increased to 500 and 1000 million, respectively. No bad effects were noticed. Rolleston (1919) reported 21 cases treated with vaccine in addition to other measures, with a mortality of 23.5 per cent.

Hector Mackenzie, Rundle, Mottram, R. S. Williams, Orr, and A. E. Williams had previously reported cases of cerebrospinal meningitis successfully treated. In that of the last named observer, the first dose contained 200 million meningococci; the second, 500 million; the third, 510 million (five-day intervals). Two more doses were given at eight-day intervals, each being 530 million. Unusually rapid and complete

recovery without involvement of the special senses took place.

The use of meningococcic vaccine has been suggested, among others, by Lewkowitz (Lancet, Sept. 6, 1924). In a case which had not completely recovered with the use of serum, he gave the patient his own freshly prepared serum by intraventricular injection, the serum having proven to be of high immunological titre from the use of vaccine. Immediate and complete recovery followed.

Vaccine in meningitis appears to be of service in particular in subacute and chronic cases where serum no longer seems effective. If a stock vaccine is used it should be polyvalent. An autogenous vaccine is, however, to be preferred.

#### **BACILLUS PYOCYANEUS.**

The *Bacillus pyocyaneus* is responsible for primary and secondary infections in various parts of the body.

Waite, reviewing the literature, found that this organism had been reported as the cause of infections in practically every part of the body, the eye and ear, respiratory and digestive tracts, serous membranes, meninges, genitourinary tract, skin, liver, bones, and joints, as well as a number of more general infections, such as abscesses in various parts of the body. The lesions may be general or localized, mild or severe.

Grace-Calvert used a vaccine for the treatment of **middle-ear disease** where the sole organism was the *Bacillus pyocyaneus*. He met with success up to a certain point, but later the ear began to discharge more freely, although the cause of the trouble was still limited to the *Bacillus pyocyaneus*.

Trimble reported 5 cases of **suppurative otitis media**; 2 were due to the

staphylococcus; 1 to *Bacillus pyocyaneus*; 1 was a mixed staphylococcus and pyocyaneus infection, and 1 contained streptococci. Good results were obtained from the use of vaccines in all except the case showing the *Bacillus pyocyaneus* in pure culture.

Kolmer reports that the *Bacillus pyocyaneus* was found in 20 per cent. of cases of suppurative otitis media discharging for four weeks or longer. This organism is believed by many to be a practically harmless saprophyte, feeding on tissues killed by some other organism. In 10 per cent. of the cases this bacillus was found from the third to fourteenth day of discharge, alone or in combination with some other organism. The results of vaccine treatment were satisfactory in these early cases and while the administration of a vaccine prepared from this organism may have been merely coincident to a rapid cure, yet he cannot agree with those who claim the vaccine to be practically without effect. On the other hand, of the 15 patients dismissed from the hospital with persistent discharging ears, in 13 the *B. pyocyaneus* was found in pure culture and the vaccine did not produce favorable results.

Groves has reported a case of *Bacillus pyocyaneus* **pyemia** in a boy of 8 years, successfully treated by vaccine. After he had been developing abscesses in various situations for nearly a year, a bacteriological examination was made and a pure culture of *Bacillus pyocyaneus* obtained. An autogenous vaccine was prepared and an initial dose of 40 million bacilli was injected, with no appreciable result. Eight days later 60 million bacilli were injected; the next day the temperature descended to normal, and

it remained so thereafter. The injections were continued at from ten- to fourteen- day intervals until four more doses had been given.

### TUBERCULIN.

Since the period during which it was almost universally condemned tuberculin has gradually come into favor, until at present it is used extensively for the diagnosis and treatment of **tuberculosis**. The exact mechanism of the curative effect of tuberculin is still subject to debate. It has been thought, on the one hand, that the products manufactured by the stimulated cells are bactericidins and opsonins, and that these act directly upon the tubercle bacilli. Another theory holds that the tuberculin stimulates the production of substances which neutralize the metabolic products of the tubercle bacilli, enabling the body cells to resist their effects and remain unharmed by them, even though the bacilli are still present and growing in the body. A more recent view is that tuberculin operates through an allergic reaction. The body cells in general, including those of the skin, are sensitized by an allergen developed in the tuberculous foci, and injection of tuberculin evokes a cellular allergic shock, with local manifestations chiefly about the site of injection and the tuberculous foci themselves. In the latter situation the resulting hyperemia and exudation is thought to do good by promoting fibrosis about the tuberculous lesions.

In the treatment of **surgical tuberculosis** the results with tuberculin have been very satisfactory. In **pulmonary tuberculosis** it is believed that proper rest, fresh air, and good food supplemented by tuberculin yield better results generally than the same measures without tuberculin. Much

skill is required in selecting the proper patients to receive tuberculin and in determining the size of the dose to be administered, the intervals between doses, and the amount of rest or exercise to be taken.

The study of **mixed infections** has received considerable attention, and mixed vaccines of appropriate composition are reported to be followed by distinct success. Caulfeild, Petit, and others have demonstrated that great benefit may follow the use of bacterial vaccines even without tuberculin.

That tuberculin is capable of doing a great deal of harm if carelessly used—that it is a two-edged sword—has been repeated so often that to those who do not have an opportunity of seeing the effects of its careless administration the saying seems trite. Nevertheless, it cannot be denied that many persons have been so impressed by the harm tuberculin may do, that their anxiety to do no harm has resulted in their doing little good.

In default of the practical application of opsonic index methods the only other indications the physician has concerning the amount of autoinoculation that is going on are the temperature record and the individual susceptibility to tuberculin as determined only by trial and error. The doses of tuberculin used at the present time follow pretty closely those worked out by Wright. Bacillen emulsion is generally administered in initial doses of about  $\frac{1}{50000}$  to  $\frac{1}{10000}$  mg., while old tuberculin is given in quantities somewhat larger. The doses are generally given at intervals of seven to ten days, and the slightest febrile or systemic reaction following a dose is taken as an indication that it was too large. The injec-

tion is usually given subcutaneously exactly as are bacterial vaccines.

**Kinds of Tuberculin.**—Almost innumerable forms of tuberculin have been presented to the medical profession. The tuberculins may be divided into three great classes: Those that contain the products of metabolism of the tubercle bacillus, those that contain substances of the tubercle bacilli themselves, and those consisting of both metabolic products and tubercle bacillary substances. The tuberculins consisting of the metabolic products of the tubercle bacillus are O. T. and B. F. The old or original tuberculin (O. T.) of Koch is prepared from cultures of the tubercle bacillus 6 or 8 weeks old, grown upon 5 per cent. glycerin bouillon. After sterilization the culture is evaporated to one-tenth its bulk. It is then filtered to remove the bacterial bodies. The resultant filtrate is old tuberculin. The bouillon filtrate (B. F.) differs from old tuberculin only in that no heat is used for its preparation. It is merely a sterile filtrate from well-grown bouillon cultures.

To distinguish them from the older preparations elaborated by him, Koch called the tuberculins containing bacillary substances, which he described in 1897, **new tuberculins**. There are two of these—the first, T. R., contains the washed residue of ground tubercle bacilli suspended in 20 per cent. glycerin. The final product is so diluted that the amount of solid substance is 2 mg. per c.c. Bacillen emulsion (B. E.) is more like the ordinary bacterial vaccines in use at present. The bacteria are treated merely by grinding in a hard-porcelain ball mill for a long time, the powder being then suspended in 50 per cent. glycerin. It is diluted

so that each c.c. of the tuberculin contains 5 mg. of powder. In stating the dosage of a tuberculin it is advisable to speak of it in quantities of the finished product only, without reference to the amount of solid bacillary substance contained in a cubic centimeter; for instance,  $\frac{1}{10000}$  mg. of bacillen emulsion means this amount of the completed tuberculin.

Lawrason Brown and others have suggested the use of a mixed tuberculin. That preferred by Brown is composed of B. E. and B. F.

*Bérancck's tuberculin* is prepared by growing tubercle bacilli on 5 per cent. glycerin-bouillon, neither peptonized nor neutralized. Upon filtration there is obtained a toxin bouillon (filtrate) and a residue. The latter is subjected to prolonged shaking with 1 per cent. orthophosphoric acid at 60 to 70° C. The tuberculin consists of a mixture in equal parts of the acid bacillary extract and the unheated toxin bouillon. Low toxicity coupled with a high content of specific substances are claimed for this preparation.

A few phthisiologists prefer to use a so-called "heterologous" tuberculin; that is, in treating infections caused by the bovine type of bacillus they use a tuberculin prepared from human tubercle bacilli, and *vice versa*.

According to the chemical and clinical investigations of Esmond R. Long (Jour. Amer. Med. Assoc., Aug. 29, 1925), the active principle of tuberculin is of protein nature. It is non-dialyzable; is not absorbed by animal charcoal; is destroyed by trypsin; is maximally but incompletely precipitated by acetic acid at pH 4.0, and is completely precipitated by saturation with ammonium sulphate. The latter precipitate can be separated into three protein

fractions: (1) A water-soluble, heat-coagulable protein; (2) a non-coagulable, alkali-soluble, water-insoluble protein, and (3) a non-coagulable, water-soluble protein. Of these, the first and third appear to be the most potent.

**The Diagnostic Reactions.**—The only tuberculin used to any extent for diagnostic reactions is O. T. When tuberculin is injected even in large doses into a person free from tuberculosis no symptoms are produced. If, however, tuberculosis is present there follows, within the course of a few hours, a rise in temperature and a feeling of general malaise. The general disturbance is accompanied by a local reaction at the point of injection, which becomes red and exhibits a swollen appearance. Tuberculous individuals react to very minute quantities of tuberculin and, when properly used, this phenomenon is of great diagnostic value. The following method is followed by Roth-Schulz:—

“The temperature and pulse rate of the patient to be investigated are carefully noted for from four to seven days, after which, in the event of these being normal or only very slightly elevated, an initial *hypodermic injection* is given of 0.5 mg. old tuberculin. If no reaction follows this in from three to four days, the same dose is usually repeated, particularly if any symptoms indicative of a mild reactions have occurred. If the temperature shows any irregularities, a longer period is allowed to elapse and the same repeated a third time. Usually, however, in the absence of reaction, the second dose is increased to 1.25 mg. This amount may be repeated after the lapse of two or three days without reaction, or the dose increased to 2.5 mg.

This maximum dose may again be repeated. The importance of repeating the same dose is emphasized, as often a merely suggestive reaction after the first administration may be followed by severe symptoms after the second dose.

“A rise in temperature of 1° F. (0.5° C.) above the previous maximum is considered positive, but great importance is attached to the development of general and local phenomena. Even in the event of only a slight rise in temperature, the development of râles where they were previously absent, or the occurrence of general symptoms, is considered positive.

“There is no danger in the test as outlined, even when incipient or latent tuberculosis is present, as the fever reaction is usually moderate and soon disappears if the patient is kept in bed a day or so. The advantage of making a diagnosis in doubtful cases before physical signs or symptoms are available cannot be over-estimated in relation to the prognosis of treatment.”

Lawrason Brown and Heise (Amer. Rev. of Tub., June, 1920) believe that the subcutaneous test with O. T. proves tuberculous infection. When accompanied by clinical and especially X-ray evidences, it signifies a lesion relatively accessible to circulatory changes and less firmly cicatrized.

**The Cutaneous Reaction.**—*Von Pirquet* pointed out the fact that, upon scarifying the skin of a tuberculous subject and applying a solution of tuberculin, there appears an area varying from a local hyperemia to an intense inflammatory reaction. Many times the reaction is characterized by the appearance of a small papule, the disappearance of which is followed by a brownish pigmentation. The

reaction is not attended with fever, malaise, or any other general symptoms.

The cutaneous method consists in putting a drop of pure or diluted old tuberculin upon the skin and then making a slight abrasion of the skin under the drop of tuberculin with a lancet, quill, or von Pirquet's "scratcher" (Schäber). Only the most superficial layers of the epithelium need be removed, just sufficient to open the superficial lymph-channels. It is undesirable to draw blood. One inch away a control abrasion should be made under a drop of 50 per cent. glycerin and 0.1 per cent. phenol in physiological saline solution. Care should be exercised not to carry tuberculin on the instrument to the control. Where large numbers of patients are vaccinated a platinum-iridium instrument that can be heated is recommended.

The value of the von Pirquet reaction is variously estimated. It is extremely delicate, and on that account often reacts with individuals who appear to be practically free from tuberculosis. However, as pointed out by Hamburger soon after the introduction of the test, "it is quite difficult to find an adult free from tuberculosis, which explains the great frequency of von Pirquet's reaction in adults." Its greatest value is in the diagnosis of tuberculosis in children.

F. Feer, in a study of "the value of cutaneous and conjunctival reactions in children" based on many observations, states that "a positive von Pirquet reaction is without doubt specific for tuberculosis. Especially valuable is the test during the first three years; after this time a negative result is of more value than a positive one. Care must be taken to distinguish the

spurious from the true reactions. Reactions which disappear in twenty-four hours are not specific."

**Characteristic Cutaneous Reaction.**—Jules Lemaire has identified or distinguished three grades of the von Pirquet reaction, as follows:—

"Feeble reaction: Hyperemic zone—4 to 6 mm. in diameter, in the center of which is a papule; the skin slightly swollen and hard.

"Medium reaction: Hyperemic zone—6 to 12 mm. in diameter; numerous papules very prominent. The skin is quite edematous throughout the area. The redness persists for several hours.

"Strong reaction: All of the foregoing conditions are very much exaggerated. The area of reaction gives a very resistant sensation to touch and the zone of hyperemia extends from 2 to 3 cm. If the subjacent edematous area is pronounced, it gives an appearance of urticaria. Occasionally at the points of scarification there is an exudate of a serous fluid."

Koeppé noticed that after the application of von Pirquet's test the enlarged axillary glands on the side of the test frequently decreased in size, while those on the other side were unmodified. He concluded that the tuberculin, entering the lymph-spaces, was carried to the lymph-nodes, where it exerted a direct curative effect. Four were treated in the same way since, with good results, and he recommends it as a therapeutic measure in all cases where the lymph-nodes are swollen and hard and the Pirquet reaction is strongly positive.

A positive response was obtained by De la Torre (*Prensa Med. Argentina*, Nov. 10, 1918) in 71 out of 171 children tested in an orphan asylum. About 20 per cent. of the infants un-

der 1 year gave a positive response, including one only 2 months old; 34.4 per cent. of those between 1 and 2; 42 per cent. of those between 2 and 5; 47.6 between 5 and 10, and 57 per cent. between 10 and 15. Of the total positive responses only 52 were obtained at the first test; 11 at the second, and the others at the third to the sixth application of the test. The first 3 tests were made by the skin technique, the others by Mantoux's intradermal method.

Finding that the Pirquet test sometimes failed to show a positive response although tuberculosis infection was practically certain, H. Grass (Beitr. z. Klin. d. Tub., May 25, 1924) developed a modified technique which yields about 15 per cent. more of positives and greatly reduces the number of ambiguous results. A small piece of sandpaper of medium coarseness is folded twice cross-wise, making a sharp edge, which is drawn with a quick, firm stroke over the skin of the arm, or of the sternum in infants, previously cleansed with alcohol. A small portion of cotton saturated with tuberculin is placed over the abraded surface and covered over with a piece of non-irritant adhesive plaster. This method also has the advantage of dispensing with instruments, of which so many children are afraid.

For the purpose of checking up the von Pirquet test with some other of the cutaneous tuberculin tests, *Mantoux's intracutaneous injection* was done by Reiss (Arch. of Pediat., Dec., 1918) on children. A solution of old tuberculin in normal salt solution, 2 minims or 0.005 mg., was used for the Mantoux; normal salt solution for the control. Nineteen of the 120 cases gave positive reactions; one

doubtful reaction was classed as negative. The von Pirquet test was never positive in the absence of a positive Mantoux. It was negative in three cases which gave a positive Mantoux. Seventeen of the nineteen positives displayed adenopathy, and of these children, only in two were the posterior cervicals enlarged. The writer concludes that the intracutaneous tuberculin test when carefully performed seemed somewhat more reliable than the von Pirquet. Tuberculous meningitis cases apparently do not respond to cutaneous tuberculin tests (four cases after repeated tests uniformly gave negative results). The presence of posterior cervical adenopathy in children strongly suggests tuberculous infection.

Happ and Casparis (Amer. Jour. Dis. of Childr., June, 1922) compared the Pirquet cutaneous and the intracutaneous tests. The latter was more sensitive; it not only permits of accurately measuring the amount of tuberculin given, but enables one to increase the amount at will. In miliary tuberculosis and tuberculous meningitis the Pirquet was positive in just over 50 per cent. If a high enough concentration of tuberculin is given intracutaneously, a positive reaction will be obtained in practically all tuberculous cases.

In an investigation of the specificity of the cutaneous and intradermal tests, Casini (Riv. crit. di clin. med., Aug. 25, 1922) found that the tuberculous react to foreign proteins of various kinds, especially of bacterial origin. The reaction to tuberculin differs, however, in being more itchy and tender, slower in developing and persisting longer, and is therefore readily distinguished.

*The Moro or Percutaneous Reaction.*  
—The following diagnostic reaction as



described by Moro has attracted considerable attention:—

"A tuberculin ointment is prepared by a combination of equal parts of old tuberculin and anhydrous lanolin. The lanolin base is selected because with this material it is possible to prepare a very concentrated ointment. The mixture is made at a temperature of from 20° to 30° C.

"Ten grams of ointment is sufficient for 100 tests. The point of application is over the skin of the abdomen or over the breast, near the mammaræ. The ointment is energetically rubbed on to the skin for one-half to one minute. The area of the part treated is about two inches. The positive effect is noted by the eruption of a granular or a papular efflorescence at the point of application."

Moro divided the reaction into three groups:—

"First.—A weak reaction. At the point of application there appear, after twenty-four to forty-eight hours, seldom later, single, distinctly red nodules, from two to ten in number, of a diameter of 1 to 2 mm. This efflorescence disappears after a few days, and at no time has caused any itching or other irritation.

"Second.—The medium reaction. At the point of application there appear, in the first twenty-four hours, numerous (100 or more) miliary or larger red nodules, about 3 mm. in diameter. The skin surrounding the eruption is intensely red. The reaction is confined to the point of application, and is accompanied by considerable itching. This disappears after a few days.

"Third.—The strong reaction. At the point of application there appear, within a few hours, 100 or more large nodules or papules, upon an inflamma-

tory base. The dermatitis associated with it is accompanied by intense itching. Many of the eruptions form an exudate and often reach a size of from  $\frac{1}{8}$  to  $\frac{1}{4}$  inch in diameter.

"The reaction is not only confined to the point of application, but extends into the surrounding areas. After a few days the papular efflorescence dries up, leaving a brownish pigmentation of the skin which remains for several weeks. General symptoms, namely, rise of temperature, etc., do not accompany the reaction.

"The strong reaction occurs seldom. In 37 positive reactions, we only observed it 3 times, 2 of these cases being scrofulous and 1 caries of the bone. The weak reaction we observed 25 times and the medium reaction 9 times in the 37 cases.

"The most distinct reaction is observed in scrofulous conditions and tuberculosis of the bones. Weaker reactions occur most often in cases of tuberculosis of the lungs.

"An important factor in determining the stage of the reaction is, without doubt, the sensitiveness of the skin."

Moro gives a table showing the value of the percutaneous reaction compared with the cutaneous vaccination of von Pirquet. In 16 cases of undoubted tuberculosis, 12 were positive with the percutaneous reaction and 14 positive with von Pirquet's reaction. In 12 cases of scrofulous conditions, 6 reacted "positive" to the percutaneous reaction and 6 "positive" to the von Pirquet reaction. In 20 cases of probable tuberculosis, 12 reacted "positive" with the percutaneous and 12 reacted "positive" with the von Pirquet reaction. Of 25 cases of non-tuberculous patients, 3 reacted "positive" with the percutaneous and 8 reacted "positive" with the von

Pirquet. Of 68 cases, 21 of children of suspected tuberculosis reacted and 4 children with manifest tuberculosis.

"The ointment reaction is strongly specific. All cases that gave a tuberculin-ointment reaction also gave the cutaneous described by von Pirquet. A positive ointment reaction without a positive von Pirquet reaction I have at no time observed. The ointment reaction is absolutely harmless. The occurrence of itching at the point of application occurs only relatively seldom."

The *Calmette* or *Wolff-Eisner conjunctival reaction* cannot be recommended owing to the danger to the eye incurred.

*Auto-urine Test.*—The "own urine" test was described by H. Wildbolz (Corresp. Bl. f. Schweizer Aerzte, May 31, 1919), and is sometimes termed the *Wildbolz reaction*. Some of the patient's morning urine is evaporated to  $\frac{1}{10}$  its original volume, passed once or twice through filter paper impregnated with 2 per cent. phenol, and 3 sets of 2 injections made on the arms, the upper 2 with 1:1000 tuberculin; 3 or 4 cm. below this, 2 with 1:10,000 tuberculin, and below the latter, 2 with a very small quantity of the evaporated urine. In an active tuberculous process, the response to the tuberculin and urine is the same, but when the process has healed, the urine response disappears while the tuberculin response continues. The only condition confusing the test is stated to be the presence of large numbers of staphylococci in the urine.

According to Kipfer (Schweiz. med. Woch., Dec. 30, 1922), who used this test in 200 cases, it is a serviceable auxiliary diagnostic measure. Stiefel (*ibid.*, July 27, 1922) stated that while a positive reaction is not conclusive, a

negative response seems to exclude active tuberculosis.

#### **Therapeutic Uses of Tuberculin.**—

The indications for the therapeutic use of tuberculin are all forms of chronic tuberculosis in their earlier stages, no matter where they are localized. **Pulmonary, glandular, ocular, urogenital tuberculosis, lupus, and tuberculosis of the bones and joints**, are all suitable for tuberculin therapy in properly selected cases. Of course, other appropriate therapeutic and hygienic measures must essentially be combined with the tuberculin treatment.

Tuberculin was found by Verheyden (Brit. Jour. Ophthal., Apr., 1918) to give good results in **phlyctenular kerato-conjunctivitis**, especially as regards photophobia, blepharospasm, lacrimation, but does not prevent relapses, although the latter when they occur are milder; the usual local treatment is also employed. **Scleritis** and **episcleritis** are more rebellious; the other etiologic factors of these affections should be eliminated before having recourse to tuberculin. One case of **iridocyclitis**, probably bacillary, recovered under local treatment and 6 injections of tuberculin. One case of **paralysis** of the third pair, of tubercular origin, with double ptosis, paralysis of the right superior rectus and slight diplopia, recovered after a relapse during the course of the treatment, which consisted of 6 injections of tuberculin (0.001 to 0.009) made during a period of 9 months.

The tuberculin treatment in 20 cases of different forms of **ocular tuberculosis** observed by Wimmer (Semana Medica, Aug. 29, 1918) illustrated the excellent results that can almost be counted on with tuberculin treatment as an adjuvant to the usual measures.

The mode of reaction in each patient should be carefully studied and the tuberculin gauged accordingly. The greater the reaction, the more cautious should be the dosage of the tuberculin. The most promising cases are those in which there is an intense reaction but without modification of the pulse, in which the congestion and the fever yield to small doses, and the weight shows a very slow but progressive increase.

The use of tuberculin is *contraindicated* in acute miliary tuberculosis, in tuberculous meningitis, in severe cardiac complications, and *perhaps* in epilepsy.

Tuberculin therapy as formerly practised by Trudeau has gained favor among American physicians, but on prudent lines and beginning with very minute doses, even where its use is clearly indicated.

M. Solis-Cohen (Med. Rec., Feb. 26, 1921) states that O. T. or T. R. administered carefully to incipient or moderately advanced cases with temperature below 100° F. injures none and improves many. It is, however, not to be regarded as a substitute for the physiologic and medicinal treatment, and should not be given to patients who are doing well on ordinary measures.

Pottenger (Jour. Amer. Med. Assoc., Aug. 26, 1922) believes that with tuberculin one can hasten the formation and increase the amount of fibrous tissue about the tubercle and produce a firmer scar in which to encapsulate or bury the tubercle bacilli. This can be done without subjecting the patient to any risk, provided the remedy is properly used.

*Methods for the Therapeutic Employment of the Different Tuberculins.*  
—Combe (Nourrisson, Jan., 1917) ad-

vocates a systematic tuberculin treatment of **tuberculosis in infants**. Excessive dosage induces anaphylaxis. He begins with  $\frac{1}{10}$  milligram and increases the dose gradually at 3-day intervals, up to 0.1 or even 0.5 Gm., testing the results with intradermal injection of always  $\frac{1}{10}$  milligram every 2 weeks. The progressive diminution of the reaction to this Mantoux intradermal test while the therapeutic dose is being constantly increased shows that immunization is effected. If the Mantoux reaction grows more pronounced, the tuberculin should be suspended.

To determine the exact dose of tuberculin for pulmonary **tuberculosis in children**, Myer Solis-Cohen (Trans. Am. Med. Assoc.; N. Y. Med. Jour., June 16, 1917) injects intracutaneously in 1 forearm, distally, medially, and proximally, respectively, 0.0000001, 0.000001, and 0.00001 milligram. If no reaction occurs, he later injects in the other forearm 0.0001, 0.001, and 0.01 milligram, and so on, up to 10 milligrams. The smallest amount producing a reaction is then given therapeutically *per os* or hypodermically. One patient reacted to 0.0000001 milligram, another to 10 milligrams, a dose a hundred million times larger.

P. H. Ringer (So. Med. Jour., Feb., 1918) urges that users of tuberculin be on terms of intimacy with the physical signs presented by their tuberculin patients; they must be familiar with the early signs of activity in the lung, whether of recent or recurrent origin. They must auscultate their tuberculin patients before practically every dose, as only by so doing will mild focal reactions be recognized and the dose governed accordingly. They must have before them a definite conception of what

tuberculin can do, of its mode of operation, and of what is desired in each particular case.

Sahli (Schweiz. med. Woch., July 1, 1920) advocates tuberculin administration by multiple *intra*dermal pricks with a special *Nadelschnepper*, thus causing a local production of antibodies (the skin being apparently far more sensitive to tuberculin than all other tissues) which assist in immunization. The same observer (Schweiz. med. Woch., Sept. 20, 1923) maintains that intracutaneous injection of *Béraneck's tuberculin* is the best and least dangerous method of specific treatment.

In 144 cases, H. J. van der Weij (Ned. Tijds. v. Gen., July 26, 1924) found the *Béraneck tuberculin* the most effective of several forms employed, including the *partigens* (partial antigens) of Deycke and Much. Tuberculin is most effective when producing little or no reaction. The dilutions of *Béraneck's H* (the undiluted tuberculin) used by the writer range from 1:10,000 to 1:100,000. The 1st 5 injections are 0.1, 0.2, 0.3, 0.5 and 0.7 c.c., while in the next 5 the same amounts of a solution 10 times stronger are used. Injections are given weekly and later twice weekly, with the dosage gradually raised up to 1 c.c. of *H tuberculin*. The special indication for tuberculin is chronic localized disease. It often reduces the tendency to catarrh and improves asthma, nervous rhinitis, dysmenorrhea and other manifestations of sensitization.

According to C. Fischer (Zeit. f. Tuberk., Apr., 1924), tuberculin is most effective when pure Koch's tuberculin is injected in a 1 to 1.5 per cent. solution in the patient's *own serum*. The pyretogenic action of the tuberculin is thus eliminated, and the initial dose of 0.001 Gm. of tuberculin

is repeated at longer intervals than is customary, *viz.*, after the end of the negative phase. No harm was observed to result from this heavy dosage.

R. Philip (Brit. Med. Jour., Mar. 24, 1923) favors the *percutaneous* method of giving tuberculin. In most cases it interferes little with the life and occupation of the patient. The actual amount of tuberculin applied, using, *e.g.*, a 25 per cent. dilution, is about 0.1 c.c. The ointment containing this is worked into the cleansed skin over an area of 1 or 2 square inches with a small sterile glass rod. This is done once weekly. The local reaction, while generally definite enough, causes little, if any, discomfort. This treatment is strongly advised at the earliest indication of **chronic glandular enlargement** in children.

Ladron de Guevara gives the *indications* for tuberculin therapy as follows: Recent onset with slight involvement, general good condition, and normal temperature; latent or larval forms; slowly advancing cases of bilateral disease which have improved under general hygienic treatment; chronic fibrocaceous phthisis. *Contraindications* are: Acute cases; extensive involvement with poor general condition; cases with multiple visceral foci; tachycardia above 120; mixed infections; high fever, and cardiac lesions.

*Dangers and Limitations.*—One of our ablest phthisiologists, Dr. Baldwin (Therap. Gaz., Mar. 15, 1918), an associate of the late Dr. Trudeau, of Saranac Lake, concludes as follows: Tuberculin is one of the most mysterious medicinal agents used in tuberculosis. It has such a powerful, explosive effect at times, which is fraught with danger, that no little study should be devoted to its action by physicians who

use it. It is regrettable that few acquire such knowledge before embarking on the experiment. The consequences of such superficial conceptions as may be prevalent are two-fold: either the tuberculin is used too timidly, or too recklessly. In both cases the patient really fails to get a fair deal. The first method has the merit of safety, but normal saline might accomplish as much. The second involves danger of harmful reactions, depressing to the patient and likely to aggravate the disease, more especially lung tuberculosis.

Tuberculin is an agent of limited application with safety when employed in *quiescent* pulmonary tuberculosis. It is not immunizing in the sense that relapse is prevented, although it may diminish the number of febrile exacerbations during the course of the disease. It is contraindicated in active, progressive pulmonary tuberculosis. It can be used with benefit in reacting doses for certain localized or circumscribed tuberculoses.

*Administration by Mouth.*—Latham, Spitta and Inman have investigated the value of vaccines and tuberculin administered by the mouth. They have tried these substances given in normal saline solution and in fresh horse serum. The doses of the vaccine, when administered by mouth, should be slightly larger. Apparently the negative and positive phases which follow the administration of vaccines by the mouth are shorter than those produced by the hypodermic method. The tuberculin used was T. R.

S. Solis-Cohen has confirmed the observation of Latham and his co-workers. He found diluted milk whey and physiological saline solution equally as valuable as the horse serum recommended by Latham as a diluent for the tuberculin. He employed a sugar of milk

trituration and directed that the dose should be taken at bedtime. His results confirmed Latham's observation that distinct reactions may occur from very small doses ( $\frac{1}{100000}$  mg.). The author states that there is an advantage in administering the dose early in the morning so that the time of the oncoming of reaction can be more readily observed and charted; but, on the other hand, the fact that a mild reaction may be sustained in sleep has also some advantages. Attention is called to the general rules of minimal doses progressively increased, with absolute rest during reaction time, which must be observed in this as in all other methods of using tuberculin. He begins with  $\frac{1}{100000}$  mg. of T. R. rubbed up with 1 Gm. of milk-sugar, and increases the dose by  $\frac{1}{100000}$  mg. until a reaction is evident. One dose is given every third or fourth day unless for some good reason, as prolongation of temperature rise, or excessive local or general reaction, its omission is necessary. After a reaction is evident, no increase of dose is made until the reaction-inducing dose has been twice repeated without causing rise of temperature. The maximum limit is fixed by the necessities of the case. Usually from  $\frac{2}{10000}$  to  $\frac{1}{1000}$  mg. is required. The author uses a highly nitrogenous and moderately fatty dietary, together with such medication as is indicated in connection with the gastric administration of the tuberculin.

K. von Ruck (Ther. Gaz., Mar., 1922) claims very favorable results from **tubercle bacillus body substances** ("endotoxins"), beginning with 0.05 c.c. and increasing according to the general reaction produced.

**Localized Tuberculosis.**—Wright classifies the cases of local tubercu-

losis which have derived benefit from vaccine therapy under the headings of lupus, tuberculous ulcers of the subcutaneous tissues, tuberculosis of the bone, tuberculous glands, tuberculous diseases of the genitourinary system, tuberculous peritonitis, and apyrexial phthisis.

In treating **lupus**, not infrequently certain of the patches are seen completely cured, while the disease in other regions remains refractory. These only partially successful results contrast unfavorably with those obtained in connection with tuberculous ulcerations affecting the deeper tissues.

In tuberculous ulcerations of the subcutaneous tissues the results from tuberculin therapy have invariably been satisfactory when given with proper precautions. Tuberculous lesions of the **lymphatic glands** seem especially favorable for treatment by tubercle vaccine, as those glands lie in the direct course of the lymph stream.

At the Westfield State Sanatorium, Mass., according to H. D. Chadwick (Boston Med. and Surg. Jour., Jan. 7, 1915), patients having **cervical tuberculous adenitis** and showing no more than 1 degree of temperature, and no other signs of active pulmonary disease, were given tuberculin treatment, the bacillen-emulsion being used. The initial dose was one millionth milligram and the course of treatment extended over a period of about 6 months until the maximum of 10 milligrams was reached. The glands decrease perceptibly in size and the area of dullness over the hilus becomes less pronounced. Surgical interference is necessary to remove only such glands as have become caseous or fibroid.

#### **Vaccination Against Tuberculosis.**

—Calmette regards as almost inevi-

table the contamination of children under 5 with tuberculosis, at least in crowded cities. If this infection remains localized in the lymph-node system—which it generally does—and if the infection is not massive, it confers on the child an immunity to reinfection or at least makes it more resistant, so that reinfecting bacilli are not tolerated; the organism then displays a characteristic tendency to dispel them at once, while it displays an equally characteristic intolerance for the products of the bacillary secretion (reaction to tuberculin). This resisting power can be measured by quantitative determination of antibodies in the serum. The antibody index shows that the resistance increases with each new infection manifested by the greater and greater tendency to rapid cheesy changes, purulent softening of tubercles and prompt expulsion of their contents. But when infection recurs again and again and in massive doses, this constant recurrence of softening and breaking down of tubercles overwhelms the system with their products, brings on the condition of actual phthisis, and the individual finishes by succumbing in spite of or rather for the very reason that he has acquired immunity. These facts point the way to effectual prophylaxis, Calmette thinks. As soon as the tuberculin first reveals that infection has occurred, the child is protected against reinfection; he has acquired immunity and resisting power enough to carry him through life if he can be protected against massive reinfections. Calmette adds that it is possible to conceive of artificially inducing this primary immunizing lymph-node action by vaccination in very young infants, by feeding them some attenuated strain of tubercle bacillus while the in-

testinal walls are still in their primal comparatively permeable condition.

Calmette, Guérin and Weill-Hallé (Bull. de l'Acad. de méd., June 24, 1924) report having conferred a manifest resistance to animals and man by means of protective inoculations of a non-tuberculogenic strain of the bovine type. The culture had been attenuated by 230 successive transplantations over a period of 13 years on a medium of potato cooked in ox-bile with a glycerol content of 5 per cent. The bacilli had become non-pathogenic for all animal species, including anthropoid apes. The organism thus attenuated has been designated as *Bacillus BCG*. Unfortunately, it can only be used for preventive purposes. It is effective only in subjects who are completely free from tuberculous infection. In those already infected it acts precisely like inoculations of any other tubercle bacilli, attenuated or virulent, living or dead, *i.e.*, it is similar to the latter in that it increases hypersensitiveness to tuberculin and to reinfections.

#### **Mixed Infections in Tuberculosis.**

—Investigations show that at least 75 per cent. of cases of pulmonary tuberculosis harbor a mixed infection. A rapid decline in the patient's condition is the usual clinical indication. Streptococci, staphylococci, influenza bacilli, and the pneumococci are frequent offenders. It stands to reason that the clinical symptoms manifested in such cases cannot be characteristic of any one invading organism, but that they must be the symptoms of a composite toxemia. Unless the patient so affected is able to elaborate sufficient antibodies he is in constant danger of further attacks or relapses. Often his condition becomes chronic. The chronicity can be explained by the fact that the patient's

resistance is sufficient to hold the infection in abeyance, but insufficient to overcome it. Such cases seem to offer a wide field for vaccine therapy and possibly autogenous vaccines afford more direct and positive means of combating the infections than stock vaccines.

When the improvement reaches a stage where the symptoms seem to be produced almost entirely by the tuberculous processes, tuberculin treatment would seem indicated and should then afford marked improvement. We must, of course, always keep in mind that hygienic treatment is a necessary accessory.

The stage of hectic tuberculosis, as Huguenin remarks, has long been known to be related to a mixed infection. There is in the lung a symbiosis of bacteria of different kinds to which the fever is to be ascribed. The question is whether the fever is due to the assimilation products and body contents of the tubercle bacillus, to the tuberculin alone, to the analogous products of the pus cocci, or to a new material formed from both together.

Leigh and Tint have had favorable results from the use of autogenous vaccines. Repeated careful examination of sputum in advanced and moderately advanced cases of pulmonary tuberculosis before or after a hemorrhage revealed the constant presence of the pneumococcus, streptococcus, *Micrococcus tetragenus* and *Micrococcus catarrhalis* in addition to the tubercle bacillus. During a hemorrhage pneumococci were sometimes the only organisms found.

The cases treated were divided into three groups:—

First.—Incipient pulmonary tuberculosis with night-sweats; frequent un-

productive coughing, with positive von Pirquet reactions and no tubercle bacilli in the sputum.

Second.—Advanced pulmonary tuberculosis.

Third.—Cases with cavity formation in one or both lungs and accompanied by frequent hemorrhages.

In preparing the vaccine the sputum was collected with great care and after washing in saline solution isolations were made on glucose-agar, blood-agar, and blood-serum. The initial dose of the vaccine was 50 million if a single organism was found, or a mixture containing about this number. The dose was doubled weekly until 200 million was reached. Following the injection of the vaccine there was local hyperemia and tenderness at the place of injection. Clinically the cough became productive in a few days and the mucopurulent expectoration was replaced by a more watery material, which was expectorated easily. Respirations became less labored and wheezy, grew easier, and gradually became normal. Night-sweats ceased, the appetite improved, patients gained in weight, and they rested altogether more comfortably. In the far-advanced cases with cavity formation the distressing symptoms did not entirely cease, but there was some relief. In all, 50 cases were studied: 20 incipient, 22 advanced, and 8 far advanced.

Minnig (Amer. Rev. of Tub., July, 1921) reported beneficial results in the use of autogenous vaccines in 8 out of 9 cases in the first stage, 10 out of 12 cases in the second stage, and 15 out of 42 in the third stage.

Cocke (So. Med. Jour., Sept., 1923) believes that in carefully selected cases autogenous vaccines are of some help in pulmonary tuberculosis,

but points out the need of careful dosage so that the patient shall get no focal reaction. Vaccines should never be used to the exclusion of other accepted therapy. Wolfe (*Ibid.*) has used a vaccine containing streptococci, pneumococci, and streptococci in 600 cases of chronic bronchiectasis, acute bronchitis and tuberculosis. He had gratifying results in tuberculosis, and feels that the improvement was due, at least in part, to stimulation of the leucocytes, particularly the polymorphonuclears.

According to Kolmer, autogenous vaccines may be very helpful in mixed infections. Sputum cultures should be made, with particular attention to the isolation of streptococci and pneumococci. If the former greatly predominate in direct sputum smears, they alone should be used. The vaccine may contain 1 billion per cubic centimeter. Extra care must be exercised in the dosage. If tuberculin is given, not more than the very slightest focal reaction is permissible. The first dose of vaccine may be 0.1 c.c., subcutaneously. Kolmer generally gives one dose each of vaccine and tuberculin weekly (vaccine on Tuesday and tuberculin on Saturday). The doses are cautiously increased until 1 c.c. of vaccine is reached. He never exceeds 10 doses of any one vaccine, results being better upon preparing fresh vaccines from time to time.

#### LEPROSY.

Rost (Ind. Med. Gaz., July, 1911) has reported on the treatment of leprosy by the use of a bacterial vaccine prepared from cultivations of the leprosy streptothrix. The report included 12 cases. They were all voluntary cases and not chosen ones. Five of them were practically cured



as far as clinical observation goes, and the others were all remarkably improved. The vaccine was injected weekly and temperature records taken, almost always showing a rise of temperature varying from 100° to 105° F. Rost is inclined to believe that the best vaccine is a sterilized six weeks' broth culture. His doses have been 1 c.c. of a 1:400 dilution of dried culture and 1 c.c. of a sterilized six weeks' broth culture. It is advisable to obtain only slight reactions in nodular cases, whereas in anesthetic cases the greater the reaction the better the result.

Most other observers have reported negative results from vaccines in leprosy.

#### **DIPHTHERIA.**

The very satisfactory results attending the therapeutic use of diphtheria antitoxin probably retarded the development of measures for the production of active immunity.

In 1903 William H. Park, Director of the Laboratory of the Board of Health, New York, showed that animals could be actively immunized with neutralized mixtures of toxin and antitoxin. In 1915 (Boston Med. and Surg. Jour., Aug. 26, 1915) the same investigator recalled the fact that 1000 units of antitoxin will confer immunity for about 3 weeks, this short duration led to efforts to increase it. Behring used a toxin-antitoxin mixture for this purpose, Theobald Smith having previously shown that it speeded and increased the antitoxin yield of horses. Individuals deprived of natural immunity were with great difficulty found to be made immune, however, while 25 per cent. of the natural non-immunes could not be made immune at all. For practical purposes, therefore, passive immunity remained

the chief measure. Bacterial vaccines had virtually failed to give immunity.

In a paper before the New York Academy of Medicine, three years later (New York Med. Jour., Aug. 3, 1918), Park gave the results of the intervening period which briefly showed not only the possibility, but the feasibility of immunizing the child population against diphtheria.

It had been found that 3 injections gave immunity in 98 per cent., 2 injections in 90 per cent., and 1 injection in 75 per cent. Most of the work had been done with 3 injections.

At birth a child had a positive immunity transferred by the mother, but this generally disappeared during the second 6 months of life, though in some, not until the end of the second year. Therefore one could not depend on a negative Schick as an indication of permanent natural immunity until this time. If after 4 years of age the child was immune, it was so through the production of the child's own cells, and the immunity was permanent. This brought up the difficulty of knowing what to do in immunizing infants. They could all be immunized without regard to the Schick reaction, and that was probably the best way except in institutions where regular tests could be made and any change from negative to positive instantly noted and acted upon. Outside of institutions it was best to immunize all children whether immune or not, and a retest should be made in 6 months or a year of all those that reacted. It depended on the family and the circumstances, but whether the child was immune or not during its first year, 3 injections would give active immunity, though a little less would develop in those already immune than in those susceptible.

Park deemed it essential to immunize the infant and not the schoolchild. The statistics of death in New York City from diphtheria in 1917 showed 133 in the first 12 months, mostly from 2 to 6 months; 274 in the second year, 186 in the third year, 152 in the fourth year, and 97 in the fifth year. At the primary school age there were only 20 per cent. that were not immune, but when one thought of the deaths that occurred before school age, the necessity for conferring immunity was very apparent. The immunity thus induced in infants lasted probably for life, for once having been instituted, it was continued as a natural immunity.

A. F. Hess (N. Y. Med. Jour., Aug. 10, 1918) stated that at the Hebrew Asylum the children given a positive Schick test were immunized by toxin-antitoxin injection. There had been no cases of diphtheria in the institution in the last 2 years. At first all cases giving a positive Schick test were immunized, but babies were found to be immune at first and then lose their immunity; thus it would seem best to immunize all individuals during the first 6 months of life in order to render the institution free of diphtheria.

Park (Proc. Soc. for Exper. Biol. and Med., Apr. 8, 1918) observed that 2 years after successful immunization the great majority of infants remained immune, not over 6 per cent. losing their immunity.

S. B. Hooker (Boston Med. and Surg. Jour., Feb. 21, 1924) has emphasized the efficacy of toxin-antitoxin and the Schick test in the control of diphtheria among young adults who are later brought into close, prolonged contact with the disease, *e.g.*, nurses and medical students. About 60

per cent. of such individuals were found susceptible to diphtheria. One series of toxin-antitoxin injections immunized  $\frac{3}{4}$ , and a 2d series given to those who had remained Schick-positive was at least equally effective, and resulted in a reduction by over 95 per cent. of clinical diphtheria in the test group.

The dosage of toxin-antitoxin mixture given is usually 1 c.c., injected 3 times at intervals of 1 or 2 weeks. Such treatment causes about 85 per cent. of susceptible individuals to give a negative Schick reaction and become immune to diphtheria. The immunity develops only in 1 to 6 months after the injections, but in at least 90 per cent. of children it lasts for more than 6 years and probably for the remainder of life (Park).

The following rules regarding toxin-antitoxin immunization are those laid down by Zingher: Infants under 6 months do not require the Schick test or active immunization, since 80 to 90 per cent. are immune to diphtheria. All children 6 months to 2 years of age should be immunized; the Schick test may be omitted, being unreliable at this age, inasmuch as a child reacting negatively may lose its natural immunity and later react positively. Children 2 to 5 years of age may be first tested by the Schick test, because after 2 years a negative reaction is reliable; but since the majority of children react positively the test may be omitted as a routine procedure and active immunization applied to all. Children of 6 to 15 years and adults should first have a Schick test; toxin-antitoxin immunization is only required when the reactions are positive. The only reliable evidence of immunity is a Schick test, to be carried out, 1 year after the immunizing injections.

Considerable importance is attached

to retesting after toxin-antitoxin immunization by C. W. Hutt (Lancet, Nov. 7, 1925) in view of the fact that the only case of diphtheria occurring among 642 children immunized was in a child who had been given the routine three injections. The boy had a severe attack, but recovered without complications or sequelæ. As to reactions after toxin-antitoxin injection, they were in practically every case negligible. In one child considerable swelling of the whole arm occurred, but she was running about the next day. A boy of 10 was reported to have had vomiting after each inoculation and to have spent the next day in bed. A third child had for a few days a small, slightly tender nodule above the external condyle.

**SCHICK TEST.**—Schick described in 1913 a method by which the susceptibility of an individual to diphtheria may be ascertained. He injects a small amount of diphtheria toxin ( $\frac{1}{50}$  of the minimum lethal dose for a guinea-pig weighing 300 grams). This is so diluted that it is contained in 0.1 mil of fluid. In the subject tested this should be injected with a very small needle, taking care that it goes directly into the skin, the flexor surface of the forearm being the chosen locality. A *small, raised, white-looking area* should result. Within 24 hours this area becomes *somewhat cyanotic, slightly edematous and reddened*. In 48 hours this passes off and a *brownish pigmentation follows*. This reaction occurs only in persons without natural antitoxin in their blood, and if such a reaction is positive, it indicates that less than  $\frac{1}{50}$  of a unit of antitoxin is contained in 1 mil of blood, and the person may be considered susceptible to diphtheria. Children sick with diphtheria give the reaction when tested before having received the antitoxic serum. The newly born rarely give the reaction; they are usually immune (93 per cent.).

According to Blau (N. Y. Med. Jour., Aug. 28, 1920), the Schick test is positive between the ages of 1 and 4 years in about 32 per cent. of normal children. It is

positive in a slightly larger ratio of measles cases, in twice as many scarlet fever cases, and in nearly 3 times as many cases of poliomyelitis. After the sixth year the positive reactions rapidly decrease, being about 10 per cent. In adults 85 to 95 per cent. of the tests are negative.

B. White (Boston Med. and Surg. Jour., Dec. 20, 1923) found in Massachusetts that slightly more than  $\frac{1}{2}$  of the school children reacted positively. The percentage of positive reactors (susceptibles) varies inversely with the number of previous contacts with infected individuals.

[See also DIPHTHERIA, Vol. IV.]

**Treatment.**—Vaccine treatment of diphtheria can be applicable only to the chronic conditions associated with diphtheritic rhinitis or unusual infections in various other parts of the body. The acute condition is so promptly and positively relieved by antitoxin that except in asthmatics and other persons known to be hypersusceptible to horse serum no other form of treatment is to be considered.

According to Bosanquet and Eyre ("Serums, Vaccines, and Toxins," 1910), vaccine treatment is of distinct value in those infections which become chronic and in which the responsible organism remains domiciled in the throat or nose for long periods after the acute symptoms have been entirely removed by the use of antitoxin. A vaccine may be prepared from the strain of the diphtheria bacillus actually infecting the patient and administered in doses of 5 to 10 million at intervals of five to seven days. One or 2 injections usually insure the disappearance of the bacilli from the local site of infection.

Forbes and Newsholme (Lancet, Feb. 3, 1912) treated patients with **membranous rhinitis** by autogenous vaccines. They give in detail the treatment of 3 patients; the intervals

between doses were five to seven days. Treatment was started in 2 of the cases on Nov. 9th with 5 million diphtheria bacilli. Subsequent doses were 10, 40, 80, 100, and 200, and the last dose on Dec. 20th was 400 million. In these 2 cases bacilli persisted in the nose even after this final dose, but the membrane had cleared up and only the nasal catarrh remained. In one of the cases the local condition seemed to be entirely cleared up by the injections. The swabs in all cases before treatment showed almost pure cultures of diphtheria bacilli, but after treatment they were scanty and mixed with other organisms.

#### **Diphtheria-bacillus Carriers.—**

Among the most troublesome conditions the health officer has to deal with is the persistence of diphtheria bacilli in the throats of persons after recovery from the disease. Typical bacilli remain in and upon the tonsils sometimes for months. Such persons must be considered a menace to the community and held in quarantine. An efficient and practical method for clearing up such conditions is highly desirable. Vaccine treatment has been tried, and with a measure of success, but failure to rid finally and effectively the focus of infection of the causative organisms seems to be one of the chief limitations of vaccine therapy. As in colon-bacillus cystitis, the symptoms may be entirely relieved and the patient symptomatically cured while colon bacilli are still present in the urine. Vaccine treatment, for this reason, has not been so uniformly successful as to make it the universal method.

Schiotz was impressed with the fact that a patient with staphylococcus sore throat placed in the diph-

theria ward by mistake had not contracted diphtheria, and also with the fact that intercurrent attacks of staphylococcus sore throat in several cases terminated positive diphtheria-bacillus findings in cases convalescent from diphtheria. Acting on the presumption that the staphylococcus was responsible for the immunity on the one hand and of the cure on the other, he inoculated altogether 6 diphtheria carriers with staphylococci, with complete success in each instance.

Catlin, Scott, and Day (Jour. Amer. Med. Assoc., Oct. 28, 1911) made use of a spray of broth culture of the *Staphylococcus pyogenes aureus* in 8 diphtheria carriers. A twenty-four-hour culture was sprayed into the nose and throat two or three times daily, all other treatment being stopped. In no instance did any harmful condition develop. Two persistent carriers failed to give a single positive diphtheria culture after the first application of the staphylococci. One person had 1 positive culture after using the spray and 1 other had 3 positive cultures. One nurse was persistently positive, and it was discovered that she had avoided using the spray as directed. More careful trial of the treatment immediately cleared her throat of all diphtheria organisms. As serious infections of the nose and throat are caused exclusively by the staphylococcus, until we know more about such things it would seem that sprays of living staphylococci should be used only with the co-operation of a bacteriologist.

Labbé and Canat (Paris méd., Jan. 6, 1917) reported very favorable results from insufflation of a powder made from the serum of horses previously injected with diphtheria bacilli killed by heat. This powder was insufflated

into each nostril of the diphtheria carriers 4 times a day. One teaspoonful of the powder in the atomizer bottle serves for 30 insufflations.

The subcutaneous use of a detoxicated diphtheria bacillus vaccine has been recommended by Fraser and Duncan (Lancet, ii, 994, 1920). Twelve injections are administered at 4-day intervals, the dose ascending from 0.05 c.c. to as much as 3.5 c.c. The vaccine used contains 100 billion bacilli per cubic centimeter.

#### ACUTE AND CHRONIC INFECTIONS OF THE RESPIRATORY PASSAGES.

Their location and function render the mucous membranes of the respiratory passages the most exposed tissues of the body. All air-borne organisms as well as those carried in food and other material taken in the mouth may come into direct contact with these membranes, often finding lodgment there and the chance for development. Considering the constant exposure of these tissues, severe infections are very rare, and under ordinary circumstances they must possess a high degree of local immunity. When for any reason vascular disturbances ensue or more profound pathological changes exist, it is not surprising that bacteria do develop. The most common infection is a catarrhal condition commonly known as "cold." The bacteria which have been found most frequently are the staphylococci, streptococci, pneumococci, *Micrococcus catarrhalis*, *Bacillus influenzae*, bacillus of Friedländer, and various organisms morphologically resembling the diphtheria bacillus.

Allen, who paid much attention to the treatment of common colds by bacterial vaccines, advised for purposes of immunization a mixed vac-

cine. He successfully treated patients with colds caused by one of the catarrhal organisms only to find that a little later another cold developed, caused by another member of this group.

T. D. Whitacre (Internat. Jour. of Surg., July, 1922) affirms that the course of colds and bronchitis is shortened by vaccine therapy and that there is preventive value in 4 to 6 injections of mixed catarrhal vaccine, given 5 to 7 days apart, beginning with 0.2 c.c. and ending with 1 c.c.—this last dose to be given 2 weeks after the previous one. In tonsillitis, vaccine therapy avoids complications such as nephritis, arthritis and endocarditis.

R. H. Babcock (N. Y. Med. Jour., Jan. 8, 1916) used autogenous vaccines prepared from the sputa. They yielded such results in 3 cases of acute bronchitis, 1 of chronic bronchitis, and 4 of chronic bronchitis with attacks of spasmodic asthma, as to warrant him in recommending this mode of therapy in preference to the old time use of expectorants by mouth. The main drawback is the necessity of several cultures and the preparation of new vaccines, should the cultures show that some of the originally found germs have disappeared or become subordinate in number to others. New vaccines should be prepared whenever the condition of the patient seems to have come to a standstill.

H. A. Cables (Lancet-Clinic, July 22, 1916) laid stress on the efficacy of vaccine treatment. He used stock vaccines of the Van Cott formula. The first dose given is a large one, to excite the formation of a great amount of antibodies. The interval between doses is always at least 4 days, and is length-

ened to a week or 10 days as improvement takes place. Codeine,  $\frac{1}{4}$  grain (0.016 Gm.) every 2 hours, is often given to procure temporary relief before the action of the vaccine is brought into play. The improvement following each dose depends upon the severity of the reaction, which is partly local and partly systemic. Great care is taken to eliminate cases of tuberculous infection.

For the treatment of influenza, especially after the disease has existed longer than a very few days, a mixed vaccine is indicated. The physician may not expect to control the many unfortunate sequels of this condition if a vaccine containing only the influenza bacillus is used.

In a study of the etiological relationship between common colds and influenza, Hitchens (Med. Rec., Feb. 17, 1912) stated that the omnipresence of the "cold" bacteria promotes the formation of antibodies. These functions being temporarily arrested or hampered by external physical conditions or by the attacks of more virulent bacteria, the treatment indicated is one capable of stimulating the formation of antibodies by the use of bacterial vaccines.

One of the first conditions treated on these principles was what he deemed to be a type of "cold," influenza. The results were encouraging, but the plan of isolating the most active agent and using the corresponding bacterial vaccine soon began to show its inadequacy. A patient treated with pneumococcic vaccine remained as susceptible as ever to the influenza bacillus, *Micrococcus catarrhalis* group, etc., and for both prophylactic and therapeutic purposes a vaccine composed of all the "cold" organisms was employed. On the other hand, it is difficult and in many cases impossible to tell which of the cold or-

ganisms may be the guilty one, and in most cases of cold at least several varieties are concerned. Hitchens, therefore, advocated for general use a mixed influenza vaccine for the prophylaxis and treatment of common colds, mixed infections of the respiratory mucosa and influenza.

A. I. Simey (Lancet, Nov. 21, 1925), discussing the prophylaxis of the common cold, referred to a report lately published of an experiment in a boarding-house of a large public school, in which each child received in the course of a year 5 injections of an anticatarrh vaccine prepared in a local hospital. The vaccine was composed of *Micrococcus catarrhalis*, *B. pneumoniae*, pneumococcus, *B. septus*, *B. influenzae* and streptococcus. The results were so encouraging that the procedure was continued regularly, and the record for 4 years showed that not one girl who had been duly inoculated missed a single day at school owing to colds or influenza, whereas of those girls who were not inoculated a considerable number were confined to bed with colds and influenza, and 2 contracted pneumonia. In this house the number of girls averaged 40, and they mixed freely with other uninoculated pupils in their class-rooms. The writer comments on the advantages of using a vaccine that is both easily procurable and made from local material.

According to C. H. Duncan (Med. Standard, Mar., 1916), autotherapy usually cures acute influenza in twenty-four hours if the following simple technique is properly employed: Mix sputum 1 dram (4 c.c.), distilled water 1 ounce (30 c.c.), in a 2 ounce (60 c.c.) bottle, shake well, and allow to stand twenty-four hours. Filter through a Berkefeld filter. Inject 20 minims

(1.25 c.c.) of the bacteria-free filtrate into the loose cellular tissue over the biceps muscle. Give no further dose until the patient ceases to improve under the preceding dose.

Major Roberts, of the Columbia War Hospital (Trans. N. Y. Acad. of Med.; Med. Record, Nov. 2, 1918), recorded a series of cases treated with the vaccines and without. These showed the value of the intravenous vaccine treatment. In one series of 86 cases without vaccine the mortality was 35 per cent., while in a series of 153 patients treated with the vaccine it was about 8 per cent. After the first injection of the vaccines, in cases in which there had been congestion and nosebleed, the latter stopped and there was less dyspnea and very little cyanosis except in the very severe cases. The vaccines were given in 3 to 4 doses of  $\frac{1}{2}$ , 1, and 2 c.c., at 24-hour intervals. One c.c. of the vaccine contained 1 million influenza bacilli and 1 million pneumococci of Types I, II, and III, 1 million streptococci and 1 million staphylococci. They started with  $\frac{1}{2}$  c.c., and at the end of 24 hours they gave 1 c.c., and 24 hours later 2 c.c. As a rule they did not get much reaction with the  $\frac{1}{2}$  c.c., though there might be a rise in temperature. Usually from the 1 c.c. dose they got a fairly definite reaction which was different from a non-specific protein reaction.

Evidence is at hand, according to J. H. Kolmer (Phila. Co. Med. Soc.; N. Y. Med. Jour., Nov. 23, 1918), indicating that the streptococcus and micrococcus catarrhalis are also concerned in the pathology of the infection, possibly not as primary agents, but as secondary factors of considerable importance. That the resistance might not be reduced, small doses of the

vaccine were given at intervals of 3 days until 3 injections were given. It would seem that the administration of the vaccine at intervals of 3 days does protect a certain number of persons against influenza, but it does not confer absolute immunity.

Eyre and Lowe (Lancet, Oct. 12, 1918), during the war, tried extensively prophylactic vaccinations against catarrhal affections. The vaccine used was prepared in 2 different strengths, the weaker initial dose being followed ten days later by the second stronger dose; in each instance the volume of vaccine administered amounted to 0.5 c.c. It was prepared from organisms contained in the secretions of purulent bronchitis and in the sputums of other catarrhal cases among the troops in England. It contained:

ORGANISMS PER 0.5 C.C.

Organism.	First Dose.	Second Dose.
Pneumococcus .....	50	100 million
Streptococcus .....	10	50 million
B. influenzae .....	10	30 million
Staphylococcus aureus ..	200	500 million
M. catarrhalis .....	25	75 million
B. pneumoniae .....	50	100 million
B. septus .....	50	100 million

This vaccine was designed to produce an artificial immunity, not only against the first three virulent organisms, which are frequently found present in fatal purulent bronchitis, but also to immunize against the other organisms most frequently found in catarrhal sputums and nasal discharges.

The following results were obtained: (a) 2081 men inoculated with the initial dose. No reaction, 2033, 97.7 per cent.; slight reaction, 42, 2.0 per cent.; severe reaction, 6, 0.3 per cent.; (b) 1627 men inoculated ten days later with the second dose. No reaction, 1607, 98.8 per cent.; slight reaction, 3,

0.7 per cent.; severe reaction, 7, 0.4 per cent. Slight reaction: Headache in twenty-four cases; temperature from 99 to 101 in fourteen; sore throat in five; neck stiffness, nausea and fainting in five. Severe reaction: above symptoms more marked and accompanied by temperatures between 101 and 104. The incidence of the influenza epidemic was appreciably less among the inoculated men than that affecting the average 1000 of the uninoculated (2 per 1000, as against 28.4 per average 1000), a result which amply justified the prophylactic use of the vaccine.

McCoy, Murray and Teeter (Jour. Amer. Med. Assoc., Dec. 14, 1918) gave the results of strictly parallel observations made to determine the value as a prophylactic of a vaccine, each c.c. of which contained:

Influenza bacilli .....	500,000,000
Pneumococci, Type I .....	500,000,000
Pneumococci, Type II ....	500,000,000
Pneumococci, Type III ...	500,000,000
Pneumococci, Type IV ...	1,500,000,000
Streptococcus hemolytic ..	1,000,000,000
Staphylococcus aureus ....	500,000,000

Two or more strains of each organism were employed in the preparation of the vaccine and the doses were  $\frac{1}{2}$ , 1, and  $1\frac{1}{2}$  c.c. respectively, at intervals of 2 days. Every alternate patient in a State insane asylum was given the vaccine, the others being untreated. Each group contained 390 persons. Inoculation was completed 11 days before the first case of influenza appeared in the institution. Of the vaccinated persons, 119 developed influenza with 23 cases of pneumonia and 10 deaths, as contrasted with 103 cases of influenza with 17 cases of pneumonia and 7 deaths among the unvaccinated.

W. F. Robertson (Brit. Med. Jour.,

Dec. 21, 1918) recommended, after using it in 100 cases, a vaccine made from the *Bacillus influenzae* in **chronic influenza** infections, the doses ranging from 0.005 to 0.1 mg. of the dried bacilli. Correct doses usually cause distinct focal reactions, while larger doses cause all the characteristic symptoms of an acute attack of influenza, showing the pathogenicity of this bacillus. The treatment should be continued over a period of 6 to 10 weeks. In protective inoculation other organisms must be included in the vaccine. The *Micrococcus catarrhalis* being the cause of severe, epidemic coryza predisposing to influenza, it must be included. Neither the pneumococci nor the streptococci should be included, however, for immunization, since these are purely secondary invaders. But for developed influenza a sensitized vaccine should be used, containing:

<i>Bacillus influenzae</i> .....	0.01 to 0.04 mg.
Pneumococci (polyvalent) ...	0.01 to 0.02 mg.
Streptococcus .....	0.01 to 0.02 mg.
<i>Micrococcus catarrhalis</i> .....	0.03 to 0.06 mg.

Bezançon and Legroux (Bull. de l'Acad. de méd., Paris, Jan. 14, 1919) found a polyvalent vaccine used by them, which contains in 1 c.c. 4 millions pneumococci to 2 millions each of streptococci, Pfeiffer's bacillus and *Micrococcus aureus*, quite harmless. They injected daily about 0.25 c.c. at a time at first, increasing the dose to 1 c.c. In this way they injected up to a total of 13 c.c. In one group of 60 repatriated prisoners with influenza, the mortality was 8 per cent., while it was 17.8 per cent. among a group of 25 not given this treatment.

Horn (Jour. Amer. Med. Assoc., Aug. 28, 1915), studying the etiology of **ozena** in an effort to determine if the



Perez bacillus was the etiological factor, removed crusts from the nose and dropped them into a tube of bouillon; after 12 hours' incubation the culture was plated and isolation made. Vaccines were prepared from these cultures (several strains), which he administered to a series of patients with improvement in some cases. He concluded that the Perez bacillus is the etiological factor in ozena. Agglutinating serum has been prepared with difficulty. He suggested the possibility of preparing a vaccine from several strains of the bacillus of ozena together with the other organisms usually found. The Friedländer bacillus, which is so frequently found in these cases, probably has no etiological significance.

Horn and Victors, who conducted some further work in this direction, are rather of the opinion that the Perez bacillus belongs closer to the typhoid-colon group than it does to the Friedländer group.

#### ACNE.

For the treatment of acne, Wright suggested the use of a staphylococcus vaccine. This suggestion was based upon the finding of staphylococci constantly in pustular lesions, and in this form of the disease the treatment was attended with considerable success up to a certain point. Some patients were apparently cured, but many were found refractory to repeated injections; the pustular condition frequently disappeared, but comedones did not appear to be influenced. It was later shown by Fleming that these patients could be brought to complete cure by the use of a vaccine containing the acne bacillus. The doses of the vaccine generally used are from 1 to 10 million, and the injections are repeated at weekly intervals. If the staphylococcus is associ-

ated with the acne bacillus in the lesion a mixed vaccine containing the same number of acne bacilli and from 50 to 300 million staphylococci is indicated.

In 1893 Unna described a bacillus which he believed to have a causal relationship to acne. He maintained that it was the only bacillus constantly present both in the comedo and in the pustule, but he was unable to cultivate it.

Sabouraud in 1897 found the same organism, but differed from Unna in believing that pustulation in acne was frequently caused by the staphylococcus. He arrived at this conclusion from the fact that staphylococci are found in the phagocytes, while he was never able to find the acne bacillus undergoing phagocytosis; also because he was never able to produce suppuration by the subcutaneous injection of even large quantities of the acne bacillus. This is the view held at present by the majority of investigators; the acne bacillus alone is present in the deeper parts of the comedo, and staphylococci, if present at all, are confined to the superficial part and are in reality a surface contamination. Sabouraud was the first to obtain cultures of the acne bacillus. He did this by inoculating material from the lesions into a special acid medium which was incubated for a long time, thus allowing the staphylococci to die out.

Sabouraud claimed that the bacillus isolated by him was the cause of **oily seborrhea** and also of **alopecia areata**, which he considered a localized seborrheic condition. He was the first to describe accurately the cultural properties of the organism, which he named "bacille de la séborrhée grasse." It is an anaërobe, although it will grow feebly under partial aërobic conditions.

The bottle bacillus mentioned by

Sabouraud and others is a large organism shaped something like a bottle, presenting an appearance very much like a yeast. It occurs in the more superficial parts of the comedone, and is found constantly in dry seborrheic conditions of the scalp or elsewhere, where its presence has been considered of great diagnostic value.

Gilchrist (Johns Hopkins Hosp. Rep., vol. ix, p. 409, 1900) was the first to obtain pure cultures of the acne bacilli directly from lesions of acne vulgaris or from comedones; he renamed the organism *Bacillus acnes*. Gilchrist found the bacillus present in all smears from 240 typical acne lesions from 36 patients. The bacillus was described as a short, thick organism in the smears, while in cultures it became longer, thicker, and branched. Irregular staining was noticed in older cultures. It does not decolorize by Gram's method and is not encapsulated.

Interest was raised in the etiological significance of the acne bacillus by the work of Fleming (Lancet, vol. i, p. 1035, April 10, 1909). He had noted that very frequently in treating a case of acne with staphylococcus vaccine there was definite improvement for a time, and then the condition remained stationary in spite of any modification in the dose or character of the staphylococcus vaccine. He then took up the study of the relation between the acne bacillus and these resistant cases, and reached the conclusion that the *B. acnes* was the cause of acne.

In most of his work Fleming used a stock vaccine; in some instances he used autogenous vaccine and in others autogenous and stock concomitantly. The stock vaccine was derived from a pustule on the face of a woman who had

had severe pustular acne for many years. She had been receiving staphylococcal inoculations at intervals of ten days for about a year. The condition had improved somewhat at first, but for some months had remained almost stationary. She then had the same stock staphylococcus vaccine combined with 20 million of her own acne-bacillus vaccine. This was followed by the appearance of fresh pustules and aggravation of existing ones. Such treatment was continued with the doses of acne bacilli varying from 5 to 10 million; in three months almost all traces of acne had disappeared. Fleming described other cases in which favorable results were obtained. He stated:

"While these cases illustrate the fact that in some cases an autogenous vaccine of acne bacillus is necessary, yet experience has shown that in the vast majority of cases great improvement has been induced by the inoculation of a stock vaccine combined with staphylococcus if an examination of films has revealed that that organism is present. The dose used has varied from 4 to 10 million, and the intervals between inoculations from one to two weeks. The guide to treatment has been the appearance of fresh lesions either during the period of low resistance following the positive phase when too long an interval has been allowed to elapse, or in the next two or three days after an inoculation indicating that too large a dose has been administered. By watching these signs and working the dose up till it just fails to show any 'negative phase' clinically one obtains the maximum benefit from the vaccine."

Walsh (Med. Press and Circ., vol. lxxxix, pp. 80-82, Jan. 26, 1910) stated that the treatment of acne is satisfactory when begun early in the disease.

The use of a *polyvalent vaccine answers well enough* in most cases. Where the chief feature is a **comedo**, acne-bacillus vaccine alone is indicated. In other cases a mixed vaccine of 200 million staphylococci and 8 million acne bacilli is used. The dose is gradually increased to the maximum with intervals of about ten days. Walsh found the treatment to yield durable results in some cases, while others recurred afterward or showed no appreciable improvement.

D. King Smith (Jour. of Cut. Dis., vol. xxiv, pp. 432-435, 1911) treated about 150 cases of acne vulgaris. The patients treated were divided into three classes: A, those with the acne bacillus alone; B, those infected with the acne bacillus and the *Staphylococcus albus*, and, C, those infected with the *Staphylococcus albus* in which practically no bacilli were present. Class A patients were treated with acne vaccine, the dose being 5 million, repeated twice a week. The results in a number of cases were good, but on the whole were disappointing. The final conclusion was that along with a general and local treatment the vaccine is useful. The results were better in Class B with a mixed vaccine, while those in Class C gave excellent results.

According to Sibley (Clinical Jour., Apr. 29, 1914), severe cases of acne often do better under vaccine treatment than comparatively mild ones; the most resistant to this treatment are usually those with abundant seborrhea, many comedones, and scanty foci of suppuration. Vaccine treatment must be continued for 6 months at least, and long after all spots have ceased to appear, when diminishing doses at longer intervals will often prevent relapses and complete a cure.

Howard Fox (Jour. Amer. Med. Assoc., Oct. 27, 1923) states while good results have been obtained with vaccines by a few investigators after patient efforts with special technique, in the hands of the majority the results, in general, have been unsatisfactory. The weight of opinion is that mixed vaccines (acne bacillus and staphylococcus) are of more value than those of the acne bacillus alone. Stock and autogenous vaccines are considered by the majority to be of equal efficiency. Whatever value these vaccines may possess is restricted to their use in selected cases, chiefly of the pustular type, or as an adjunct to other methods of treatment. The action of vaccines is slow and often temporary.

In **acne indurata** and some forms of **cystic acne**, Engman (Jour. Amer. Med. Assoc., lxxvi, 176, 1921) has obtained benefit from stock acne bacillus vaccines. The early doses are 3 to 5 million, repeated at 5 to 7-day intervals according to the reaction, which consists generally in the appearance of a few new lesions within 48 hours after an injection. On the third day after each injection local hyperemia is induced with hot towels or by manipulation of the lesions. Where new lesions appear after the third day, a few doses having been given, the amount is increased to 7 to 10 million, and this is kept up until the desired results have been obtained, after which the intervals are progressively lengthened to 4 weeks. Appearance of many new lesions within 48 hours after a dose is an indication for lessening of the dose and increase of the interval.

Strickler and Schamberg (Trans. Amer. Assoc. of Immunol.; Med. Rec., July 13, 1918) found complement fixa-

tion present in 63 per cent. of cases with an antigen prepared from colon bacillus isolated from the intestinal tract of the patient. It was resolved to treat 50 cases with no other means than vaccines prepared from an autogenous colon bacillus. These cases were controlled by cases treated by other methods,—vaccines from other germs, therapeutic and hygienic measures. The *B. coli* vaccines were found to possess better curative effects than any other mode of treatment. It was likely that at puberty, when there was great developmental activity, there was liability to infection from the intestinal tract. The activity of the intestinal organisms would then produce noxious effects. The complement fixation tests would incriminate especially the colon bacillus.

#### PERTUSSIS.

Bordet and Gengou have shown that whooping-cough is due to a small organism resembling the influenza bacillus. It is more easily isolated during the earlier than the later stages of the disease. The *B. pertussis* is a constant factor in the disease and the symptoms are probably due to toxins and endotoxins liberated by it. As in other inflammatory conditions of the upper respiratory passages, it is more than probable that secondary infections play a prominent part after the condition has established itself.

Paul Luttinger (Jour. Amer. Med. Assoc., May 19, 1917) summarized the results of 180 physicians to whom the Bureau of Laboratories of New York had supplied pertussis vaccine over a given period of time, and also the results obtained in the City whooping-cough clinic. The results obtained at the whooping-cough clinic warranted the routine administration of pertussis

vaccine for both curative and prophylactic purposes. The best time to institute vaccine treatment is the first and second week of the paroxysmal stage. When the proper vaccine is given and the method of the department is employed, the disease is materially reduced in duration and severity.

Rosenthal (Medical Council, June, 1918) states that the use of vaccine in the treatment of pertussis has proven to be entirely satisfactory in from 80 per cent. to 85 per cent. of his cases, and that the earlier in the course of the disease the treatment was begun, the more positive the result. He urges large doses, not less than 1 billion as the initial dose, increasing 1 billion every second day, unless a reaction is produced, until 3 or 4 billion are given, continuing this dose every second day until well. Usually from 5 to 8 doses will be found necessary. He found the best vaccine to be mixed stock vaccine containing Bordet-Gengou bacilli, pneumococci, micrococci catarrhalis and streptococci.

According to Huenekens (Amer. Jour. Dis. of Children, July, 1918), pertussis vaccine from 2 to 3 months old, employed in very large doses, 1 billion and over, immunizes in only 12.5 per cent. of cases. Two to 4 weeks old vaccine confers immunity in from 25 to 75 per cent. of cases. Freshly prepared vaccine, employed in the same dosage, shows evidence of antibody formation in 94 per cent. of cases. When used in still larger doses, 1, 1½ and 2 billion, 100 per cent. positive reactions are obtained. The antibodies are demonstrable within one week after the last injection. Pertussis vaccine less than 1 week old should be employed, without preservative. The most effective dosage is 1 billion, 1½ billion and 2

billion, given on alternate days, for three doses. The vaccine is most effective as a prophylactic, but should be of great value in the early catarrhal stage of pertussis. In doubtful cases of pertussis the vaccine should be administered before an exact diagnosis can be made, especially during an epidemic.

Bloom (Arch. of Ped., Aug., 1925) reports that of a series of 383 children immunized with pertussis vaccine since 1916, 70 per cent. of whom were exposed, only 4 cases developed. Curative treatment was given in 458 cases. The vaccine used was freshly prepared, *i.e.*, not more than one month old; he prefers to use it within ten days after preparation. The vaccine contained 5 billion pertussis and  $3\frac{1}{2}$  billion influenza bacilli per cubic centimeter. For prophylaxis 1 c.c. is given on alternate days for 3 doses. The same amount is also given every second year if the complement fixation test justifies it. For curative purposes, 1 c.c. is given as the initial and subsequent doses provided there is no marked reaction. If such reaction does occur, the amount is reduced. The injections are given on alternate days until one of the marked symptoms shows a remission, then every 3 or 4 days until the pronounced symptoms, coughing, vomiting, etc., are on the wane. Usually no drugs are given when the vaccine therapy is used. Occasional sedatives are, however, prescribed. In all cases iodides are administered, when the vaccine has been discontinued.

The conclusion he reached after 13 years' observation was that the procedure is the most efficacious in all respects as a preventive. The prophylactic treatment has great possibilities in asylums, schools, public institutions, and in the limiting of disastrous epidemics.

### ASIATIC CHOLERA.

The idea of vaccine prophylaxis of Asiatic cholera has been combated almost from its inception, but it has little by little gained favor until at present there is widespread belief in its efficacy.

The *method of Haffkine* involves the use of two vaccines, a weaker and a stronger. The weak vaccine is obtained by growing the bacteria on agar at a temperature of 39° C. in a current of air. The stronger vaccine is prepared by passing the vibrios through a series of guinea-pigs until a virus is obtained which is invariably fatal to these animals within eight hours. Injections are given hypodermically in the flank, and an interval of five days should separate the two inoculations. The degree of protection afforded by the vaccination is said to be proportional to the severity of the symptoms caused by it. Reporting his experiences in Calcutta and Lucknow, Haffkine gave the following figures:—

Population.	Cases.		Deaths.	
	Total.	Per cent.	Total.	Per cent.
Non-inoculated	1735	174 10.63	113 6.51	
Inoculated	500	21 4.20	19 3.80	

C. Dopter (Paris médical, Jan. 2, 1915) called attention to the efficiency of anticholera vaccination in the Balkan wars. Whereas the incidence of cholera among 14,332 unvaccinated officers and enlisted men was 5.75 per cent., that among 21,216 men vaccinated once was but 3.12, and among 72,652 men vaccinated twice, 0.43, according to Arnaud. In the civil population of Greece, Cardamatis reported percentages of 2.12, 0.26, and 0.01, respectively. The vaccine used in these cases had been prepared at the Pasteur Institute in Paris and consisted of cultures on agar heated to 60° C. for 1 hour. The writer considers 3 injections at 5-day intervals essential if immunity

is to be acquired. Doses of 1, 1.5, and 2 c.c., respectively, should be administered.

Konrádi (Zentrallbl. f. Bakt., Part I, p. 339, 1916) states that after vaccination the blood will show agglutination for about a year. An annual dose of 0.5 c.c. suffices. Konrádi employs *Kolle's method* of preparation of cholera vaccine. The bacterial emulsion is heated for one hour at 55° C. One-half per cent. phenol is added. One c.c. of the emulsion contains 2 mg. of culture. The first dose is 0.5 c.c. An additional 1 c.c. is injected after one week. The symptoms are slight and usually disappear within two days.

H. E. Keisten (Munch. med. Woch., May 21, 1918) has noted that the effect of the vaccination does not last for more than 5 months, so that it should be repeated before the lapse of that time. At the beginning of an epidemic subjects formerly vaccinated may be again vaccinated even when they already show the early symptoms of cholera. There need be no fear of a negative phase. Quite the contrary, revaccination has seemed to give very happy therapeutic results.

[See also *INTESTINES, DISEASES OF: CHOLERA*, Vol. V.]

### **BUBONIC PLAGUE.**

Bubonic plague is historically one of the most interesting of the infectious diseases. Epidemics have occurred in all parts of the world, carrying off millions of people. The causative organism was discovered by Yersin (1894). Roux, with Calmette and Borrel, made the first trials to vaccinate animals with heated cultures. Inspired by the work at the Pasteur Institute, Haffkine prepared his "plague prophylactic" and obtained permission from the British government to use it in India. His

method is as follows: Plague bacilli are grown in broth culture for about six weeks. A few drops of oil or clarified butter are put upon the surface of the fluid. The bacteria attach themselves to these and hang down in the broth in the form of stalactites. The flask is shaken every few days to cause the bacteria to fall to the bottom of the fluid and more stalactites develop. It is believed that this method greatly increases the amount of growth. The bacilli are then killed by exposing the culture to heat (65° to 70° C.) for one hour. Haffkine at first added no preservative, but later used a small percentage (0.5 per cent.) of phenol. At present the method in use at the Pasteur Institute is more like that employed for the preparation of other bacterial vaccines. The cultures are grown on agar for about twenty-four hours and suspended in saline solution. They are killed by heat, and 0.5 per cent. phenol is added to them. The number of bacteria contained in the vaccine is not standardized by counting; an effort is made to have the suspensions uniformly turbid. The dose of Haffkine's original vaccine is 3 c.c. for an adult man, 2 to 2½ c.c. for women, and smaller doses for children. It is given by subcutaneous injection. Local and constitutional symptoms of moderate severity may follow. There is redness and swelling at the point of inoculation and sometimes a rise of temperature of 2° or 3°. These symptoms subside within twenty-four to forty-eight hours, and do not, as a rule, necessitate the abandonment of ordinary occupation. A second injection after eight or ten days is recommended.

According to Bannerman, the injection does not aggravate an attack even if made during the incubation period.



ease curtailed. In a later paper, the same observer (Brit. Med. Jour., Nov. 11, 1922) reaffirmed the value of vaccine. It should not, however, be given in acute conditions in which autogenous toxins are already numerous. The ideal is a combination of anti-toxic serum and the vaccine.

Chiriaco (Pediatria, May, 1918) in relating 3 cases, reiterates his statements as to the remarkable curative value of the Di Cristina-Caronia vaccine in the treatment of Malta fever. No time should be wasted on quinine, dieting and intestinal disinfectants. The vaccine should be given at once, as the patient grows worse under the other measures until irreparable damage results. He administers it by intramuscular injection. The results were always certain and extremely effectual.

#### DYSENTERY.

Infantile dysentery is one of the most fatal conditions affecting children under 1 year of age. The greatest number of cases occurs during July, August, and the early part of September. Lucas and Amoss (1911) employed vaccines *prophylactically* in children under 2 years of age.

Castellani (Brit. Med. Jour., Feb. 26, 1916) deems dysentery vaccination of great importance practically. Since 1912, he has prepared a mixed dysentery vaccine, and also a vaccine containing the mixed vaccine plus typhoid, paratyphoid A, paratyphoid B. Dysentery vaccine of this type should be prepared with a carbolic salt emulsion from agar cultures without heating, or peptone water cultures. Many strains of Shiga-Kruse bacillus should be inoculated in rabbits, and the least virulent, provided it be rich in antigen, should be kept permanently as a stock

culture to prepare the vaccine. Broth cultures should never be used.

The not infrequent serious consequences resulting from the use of dysentery vaccines led Leonard Rogers (Brit. Med. Jour., Jan. 1, 1916) to try the effects of sensitized vaccines. The vaccines were stock ones of Shiga or Flexner strains sensitized with the Lister Institute antidysenteric serum. The single doses of these vaccines never exceeded 100 million. In most cases the results were very satisfactory.

In an experimental study of vaccination against dysentery by the oral route, Besredka (Presse méd., Aug. 15, 1918) found that when rabbits are caused to ingest killed cultures of the dysentery bacillus, the same clinical and pathological manifestations are produced as result from the living virus. A very light attack, induced by ingestion of heated bacilli, suffices to render the animal refractory to infection by living and virulent bacilli. The immunity is such that the animal is enabled to withstand, by intravenous inoculation, a dose of the virus which kills the control in twenty-four hours. Besredka believes the procedure worthy of trial in man both for prophylactic and curative purposes.

Autogenous vaccine was used successfully by Bergell and Bonnin (Deut. med. Woch., Aug. 18, 1922) for the cure of 5 *carriers* of the Shiga-Kruse type of bacilli, given subcutaneously on successive days in ascending doses of 5, 10, 20, 30, 40, 50, and 60 million organisms. When reactions occurred, the next dose was postponed for 3 or 4 days. In but one case did the bacteria reappear after 3 months, necessitating further injections.

For curative purposes Nolf has reported good results from injection of heated vaccines, starting with a dose



of 1 million bacilli and increasing up to 5 or 10 billions. Still better results were obtained from *intravenous* injections of vaccine, beginning with 10,000 bacilli, next 30,000, next 50,000, then 100,000, and so on up to 500,000 or more. These injections were given at four-day intervals. Rapid improvement occurred, and all but 2 of 52 patients recovered.

### GLANDERS.

Bristow and White have reported a case successfully treated with vaccine. The initial dose was 10 million, and after fourteen injections at intervals of four to nine days a maximum of 300 million was reached. While the injections were followed by local and febrile reactions, no untoward effects were noted, and the course toward recovery was consistently favorable.

Cramp (Jour. Amer. Med. Assoc., May 13, 1911) had a case of **chronic glanders** in man treated with vaccine, apparently successfully, since the patient had remained free from the disease for a period of eighteen months. The vaccine was estimated to contain 14 to 20 million bacilli per cubic centimeter. The injections were given from four to seven days apart and a temperature reaction followed nearly every dose. After about three months' treatment all wounds healed and the patient's general health was excellent. He was given 5 more injections, however, at fourteen-day intervals.

Zieler (1920) has reported another case successfully treated with autogenous vaccine.

According to Kolmer, a dosage of 0.1 c.c. of a vaccine containing 1 billion germs per cubic centimeter may be utilized. Increasing amounts may be injected at intervals of five to seven days.

### DISEASES OF THE EYE.

The treatment of eye diseases by serums and vaccines differs somewhat from similar treatment of diseases in any other part of the body on account of certain anatomical peculiarities.

The cornea and vitreous normally have no blood-vessels, and are only feebly nourished by lymph; the lymph-circulation is not free, especially in the intrinsic parts of the eye-ball; this is exemplified by the rarity with which malignant growths of the interior of the eyeball give rise to secondary deposits in glands before the growth, by direct extension, has spread outside the sclerotic coat. Again, in those parts of the eye where there is a supply of blood-vessels the amount of blood in these vessels varies due to the increasing movements of the eye and its parts—the iris, ciliary body, etc. These movements are of importance when the eye is infected, as they cause the liberation of bacterial substances, toxins, etc., into the blood-stream. In the treatment of eye infections, the use of autoinoculation methods is essentially unsatisfactory, and in using vaccines it is necessary as far as possible to prevent autoinoculation by keeping the diseased part at rest. Should autoinoculation occur while vaccine inoculation is being carried out, substances of unknown amount may be set free in the blood-stream at unfavorable times, interfering with regulation of the dosage.

Since the area infected is so small there is less danger of a general toxic reaction from an overdose of vaccine, and on account of the limited blood- and lymph- supply relatively smaller amounts of bacteriotropic-carrying fluids are brought to the infected area. Relatively larger doses of vaccine may therefore be administered.

**Tuberculous Infections.**—The treatment of tuberculous conditions of the eye has been about as successful as the treatment of localized tuberculous infections in other parts of the body. The lesion may be secondary to pulmonary tuberculosis, in which case the infecting organisms are probably of the human type; it may also be secondary to tuberculous cervical or mesenteric lymph-nodes. In the latter the bacilli may be of the bovine type. This differentiation is considered of importance in treatment by Spengler, Raw, and others, who believe their results are better when they use the heterologous tuberculin. Bacillen emulsion seems to be the tuberculin preferred by the majority of English writers, although other preparations have given equally good results in the hands of others. The initial doses should be small ( $\frac{1}{80000}$  to  $\frac{1}{10000}$  mg. according to Wright) and increased gradually over a long period of time. The tuberculin should never cause a temperature reaction.

C. L. Rumsey (Jour. of Ophth., Otol. and Laryng., Feb., 1923) advocates consideration of tuberculin treatment in all obstinate cases of **phlyctenular conjunctivitis** and **phlyctenular keratitis** with a tuberculous history. Infinitesimal doses are indicated, avoiding the slightest local or general reaction. Tuberculin T. R. causes the least violent reaction.

Verheyden (Brit. Jour. Ophthal., 223, April, 1918) urges the more frequent use of tuberculin in **strumous eye affections** involving the conjunctiva, cornea, iris, ciliary body, sclera, and choroid, and in tuberculous paralysis of the third nerve. A number of cases are detailed in which this treatment was highly satisfactory. Concomitant use of dionin and sub-

conjunctival injections of saline solution is useful.

Gardini (Cronica Medica, Oct., 1918) emphasizes the long continuance of the tuberculin to ward off a relapse. A focal reaction always occurred in the eye affected. He began with  $\frac{1}{10000}$  mg. and very slowly and tentatively increased the dose to 1 mg. as the maximum, with 4 or 5 days' intervals. One patient had had **keratitis** for 2 months and it improved to a clinical cure under tuberculin treatment.

According to L. S. Mace (Cal. State Jour. of Med., June, 1923), cases of tuberculous **iritis** respond promptly to the judicious use of a potent tuberculin. He prefers Koch's old tuberculin because of its stability. The high dilutions should be used when not older than one week, while for dilutions down to the third decimal point tuberculin 1 or 2 months old may be employed. The more serious the eye process appears, the smaller must be the initial dose, as it is important to avoid all but the mildest reaction in diagnosis, and all reactions in continued treatment. The dose is usually not smaller than 0.0005 mgm. When a point is found at which a reaction appears locally, manifested in a few moist râles at the lung focus and slight reddening of the eye, the treatment is begun with gradually increasing doses and continued for several months.

**External Infections.**—*The Lachrymal Sac.*—Acute infections, especially those caused by the streptococcus, do not yield readily to vaccine therapy; but chronic infections, particularly those pneumococcic in type, yield readily, as a rule. **Chronic staphylococcic infections** also give good results when treated by stock prepara-

tions. Allen had success in treating with vaccines cases of **dacryocystitis** due to the streptococcus.

*Disease of the Eyelids.*—The *Staphylococcus aureus* is the cause of many varieties of chronic and recurrent disease of the lids. **Blepharitis** is usually due to errors of refraction, but when this is corrected staphylococcic vaccine is often an important adjuvant. **Chalazions** and **hordeola** which show a marked tendency to recurrence have been cured by a three months' course of treatment by staphylococcus vaccine. Mayon treated 4 cases of acute **styes** associated with phlyctenules and corneal ulcers, in 1 of which a complete cure was obtained; in the other 3 there was a temporary relief, followed by recurrence. He also quotes cases of styes and recurrent **tarsal cysts** cured by one inoculation.

*Conjunctivitis.*—Many acute cases of ordinary conjunctivitis clear up rapidly by the use of antiseptics. Allen, however, recommended vaccine therapy in treating the condition when caused by the pneumococcus, streptococcus, coli, or pyocyanus. **Gonococcal conjunctivitis** is of grave prognosis, and here vaccine is of value. [See *ante*, section on *Gonococcus* infections.]

In a series of cases of ocular tuberculous manifestations excellent results were obtained by R. B. Metz (Cleveland Med. Jour., Sept., 1916) from the use of tuberculin in graded doses. It caused apparent cure or marked improvement in 5 cases, including 2 of **phlyctenular conjunctivitis**.

*Chronic Conjunctivitis.*—Cases due to the diplobacillus of Morax or the Friedländer bacillus have been benefited by vaccine treatment.

*Phlyctenular Ophthalmia.*—Mackey has reported favorable results from

staphylococcic vaccine in a case of **phlyctenular keratitis** and **pustular episcleritis** of long standing with many recurrences. Gradle observed 9 cases of phlyctenular infection due to the staphylococcus, with satisfactory results from staphylococcus vaccine in all.

*Ulcerations of the Cornea.*—According to Bryan, infections of the cornea are most commonly due to:

1. *Staphylococcus*. Vaccine treatment is favorable.

2. *Pneumococcus*.

- (a) **Hypopyon ulcer**. Vaccine treatment gives a fair measure of success.

- (b) **Ulcus serpens**. Vaccine treatment usually gives good results.

- (c) **Hypopyon keratitis**. Usually the primary cause is tuberculosis; here tuberculin is indicated.

- (d) **Keratomalacia** (a form of gangrene affecting the cornea in children enfeebled by wasting disease). Vaccine treatment is unfavorable.

3. *Streptococcus*. Usually very virulent.

- (a) **Hypopyon ulcer**.

- (b) **Pseudomembranous ophthalmia** in children. Serums are probably preferable.

Allen treated 2 cases of pneumococcal **corneal ulcer** with perfect results; from another patient he isolated a small unidentified micrococcus, an autogenous vaccine was given, and this resulted in healing of the lesion. Allen found the pneumococcus to be the infecting organism in 3 cases of **hypopyon**. Treatment with autogenous vaccine cured 2 cases and improved the other one.

In *postoperative infections of the eye* excellent results have been obtained with vaccines.

In **internal infections** of the eye due

to pyogenic organisms, valuable results have been reported when a correct diagnosis was possible. Often when the condition is secondary to skin abscesses, puerperal infections, pleuropneumonia, etc., the causative organism is the staphylococcus or streptococcus. Another variety of metastatic infection may be due to pyorrhœa alveolaris, where the staphylococcus or the pneumococcus is the infecting agent. In all these cases, vaccines can be obtained from the primary lesions. When, however, there is no obvious lesion elsewhere the difficulty of obtaining cultures arises. In **iridocyclitis** cultures have been made from the aqueous humor after paracentesis by Mayon. He isolated staphylococci. Weeks treated a case of **gonococcal iritis** successfully with a stock vaccine, and mentioned 1 of severe **gonococcal uveitis** treated by Posey, all of which improved. Other workers have isolated streptococci.

#### OTITIS MEDIA.

Weston and Kolmer (Jour. Amer. Med. Assoc., April 15, 1911) have made some valuable observations concerning the treatment of otitis media following scarlatina. They believe otitis media offers good hope for success by vaccine treatment. In a series of 406 cases the discharge first appeared on the following day of the illness:—

Days of illness.	No. of cases.
1 to 5 .....	27
5 to 10 .....	97
10 to 20 .....	155
20 to 35 .....	81
35 to 49 .....	35
49 to 84 .....	11

Vaccine treatment was commenced according to the following table, reckoning from the first day of the onset of the otitis media as indicated by the presence of discharge:—

Time of discharge.	No. of cases.
Third to seventh day .....	6
Seventh to fourteenth day .....	33
Second to third week .....	21
Third to eighth week .....	28
Eighth to fourteenth week ..	10
Four years .....	1
Ten years .....	1

The best results were secured when cases were reported on the third day of the discharge. This enables one to watch the patient for a day or so; take a culture; consume five or six days in isolating the organisms and preparing the vaccine. If at the end of this time the patient's general condition was fair and he was free of fever, nephritis and toxemia, a dose of vaccine was administered. If his condition was not favorable, the vaccine was put aside in a refrigerator. If at the end of ten days his condition warranted commencing the treatment, the first vaccine was not used, for frequently a reculture showed a different organism or the presence of an additional offender. A reculture was made from the discharge and another vaccine prepared.

"In many cases, an ear cultured three to four days after the onset of discharge will show the *Staphylococcus aureus*, while on reculture at a later date the *Bacillus pseudodiphtheriæ* will be found. Most of the long-standing cases yield *Bacillus pyocyaneus*, and repeated culturing can secure nothing else.

"Cases cultured on the third or fourth day of discharge show the *Staphylococcus aureus* in many instances. A vaccine prepared of this organism usually gives good results. A week or ten days later it is often replaced by the *Bacillus pseudodiphtheriæ*, or this organism is found in addition.

"A vaccine prepared from streptococci gave quick and favorable results

each time. It was found alone or in combination in 11 per cent. of cases.

“The initial dose for the average patient 10 years of age was about as follows:—

	Million.
<i>Staphylococcus aureus</i> and <i>albus</i> . . . . .	15 to 40
<i>Bacillus pseudodiphtheriae</i> . . . . .	30 to 50
<i>Streptococcus pyogenes</i> . . . . .	5 to 10
<i>Bacillus pyocyaneus</i> . . . . .	50 to 80

“It is well to give a small dose at first and note the extent of the reaction. This reaction will be a good guide for determining the size of the succeeding dose. Doses were repeated every five to eight days. In our earlier cases they were given at shorter intervals, but results did not warrant the continuance of the practice. Succeeding doses were increased by 5 to 10 million if necessary. Following the administration, the majority of patients develop a temperature varying from 100° to 102° F. in about eight hours, gradually reaching normal in twenty-four to thirty-six hours. We have seen the temperature fall a degree or so to subnormal after an injection, reaching normal at the end of twenty-four hours. A second dose should not produce so much fever, and when doses are properly selected, the temperature reactions are quite conspicuous, each being lower than the preceding, as the patient's system is charged with an increasing quantity of opsonins, until finally no fever follows the administration.

“At the present we can estimate the value of the vaccine treatment by considering the time required to accomplish a cure under the usual form of treatment and that required under vaccines; also by the number of patients dismissed at the expiration of three to four months with ears still discharging. To determine this the records of the

hospital have been studied and the results tabulated (Woody):—

	Usual treatment. Cured.	Vaccine treatment. Cured.
1 to 10 days . . . . .	3.24%	22%
10 to 20 “ . . . . .	7.47%	22%
20 to 30 “ . . . . .	11.69%	21%
30 to 40 “ . . . . .	17.86%	8%
40 to 60 “ . . . . .	19.15%	4%
60 to 90 “ . . . . .	9.41%	4%
90 to 120 “ . . . . .	2.28%	1%
Dismissed with ears still discharging ..	13.96%	15%
Died, ears still dis- charging . . . . .	14.94%	3%

“This table demonstrates that under vaccine treatment 21.99 per cent. of cases are cured in from one to thirty days as compared with 7.46 per cent. under usual treatment in the same period of time.”

Brown and Palfrey (N. Y. Med. Jour., Aug. 23 and 30, 1919), in reporting their experience during the influenza epidemic, studied 45 cases of otitis media occurring on the service of Major C. F. Adams. Pneumococci were present in 20 cases. Eight of these yielded in pure culture: Type I, 1 case; Type II, 1 case; Type III, 4 cases; Type IV, 2 cases. The other cases had staphylococcus associated in 5 cases; non-hemolytic streptococci in 3 cases.

Hemolytic streptococci (pure culture).	3 cases
Non-hemolytic streptococci (pure culture) . . . . .	1 case
<i>Streptococcus viridans</i> (pure culture) . . . . .	1 case
<i>Staphylococcus albus</i> (pure culture) . . . . .	10 cases
<i>Staphylococcus aureus</i> (pure culture) . . . . .	4 cases
<i>M. catarrhalis</i> . . . . .	1 case
Diphtheroid bacilli . . . . .	1 case
<i>B. influenzae</i> . . . . .	1 case
<i>M. tetragenus</i> . . . . .	1 case
<i>B. coli</i> . . . . .	1 case

Autogenous vaccines were used by U. Tassi (Arch. ital. di otol., Feb., 1923) in 9 cases of acute otitis media, 9 of chronic otitis, 7 of acute suppuration of the tympanum with incipient mastoiditis, 3 of otitic meningitis, and 4 of furunculosis of the external meatus. Injections were made on alternate days, except in meningitis cases, in which the interval was 30 hours. In preparing the vaccine preference was given to the microörganism present in largest numbers. In furunculosis of the meatus the results were brilliant, obstinate cases being cured in 4 to 6 days. In acute otitis the duration of the disease was appreciably reduced by the vaccine. Five out of the 7 cases of incipient mastoiditis recovered under vaccine in 8 to 15 days, operation being required only in 2. In 2 cases of non-suppurative otitic meningitis, results were so striking as to commend this treatment for all such cases. The vaccine had been prepared from cultures of the cerebrospinal fluid. The third case was one of diffuse purulent leptomeningitis with encephalitis, and the vaccine had no effect. The same was true of the 9 cases of chronic otitis.

#### PYORRHŒA ALVEOLARIS.

Chronic suppuration of the alveolar margins, pyorrhœa alveolaris, also known as Riggs's disease, may with advantage be treated by means of vaccine prepared from the infecting organisms isolated from the pus.

For ascertaining the kind of bacteria present in the pus much can be learned by films stained either by Gram's or Leishman's method. The following bacteria can be readily recognized by their morphological forms: *Leptothrix racemosa* of Vincentini, the *Bacillus fusiformis*, the three varieties of mouth

spirochetes, a large number of organisms belonging to the diphtheroid group, diplococci, streptococci, streptobacilli, yeasts, and various forms of leptothrix and the *Bacillus necrosis* are also found.

Whenever possible autogenous vaccines should be prepared. The choice of a stock vaccine should be based upon a very careful bacteriological examination. The best results seem to have been obtained with comparatively small doses (7 to 50 million) administered at intervals of seven to ten days. Constitutional disturbances are rare; occasional vomiting, acute headache, and general malaise may be noted. In this condition the mouth is a septic cavity; the teeth are coated with tartar and impregnated with organisms which must necessarily re-infect the gums. Inoculations cannot be expected to attack these superficial bacteria; neither can they be expected to remove dead tissue. Local surgical treatment and antiseptic mouth-washes are therefore indispensable accessories.

C. P. Brown (N. Y. Med. Jour., Dec. 20, 1913) was unable to attribute an etiological rôle to any of the organisms isolated in a series of 41 cases. The following organisms were found in these cases:—

Hemolytic streptococci .....	30 cases
<i>Streptococcus viridans</i> .....	23 cases
Non-hemolytic streptococci ....	28 cases
<i>B. influenza</i> .....	19 cases
Pneumococcus .....	27 cases
Diphtheroid bacilli .....	22 cases
<i>M. catarrhalis</i> .....	30 cases

Some showed more than 1 member of the group of Gram-negative cocci. Diplococci (Gram-positive) were present in 13 which grew only in pairs in serum-dextrose bouillon, but which could not be shown to be pneumococci. *M. tetragenus* was present in 9. Following were other findings:—

Gram-negative bacilli .....	17
Staphylococci .....	15
Sarcina .....	3
Yeast .....	1
Leptothrix .....	3

Blood agar was used for the isolations. Autogenous vaccines were prepared and the results from their use were reported in papers by Joseph Head.

Joseph Head (Trans. Amer. Assoc. Immunol.; Med. Rec., July 13, 1918), who has had greater experience in this connection than probably anyone, states that he formerly gave large doses of mixed germs. He found, however, that some patients got undesirable symptoms with a dose as low as 30,000, and he has proved that the tolerance of some patients should be carefully ascertained. He concludes that it is better to keep the injection below the point of getting reactions. He therefore begins with small doses, which, if borne well, are increased. Reactions are of various types, and sore throat and colds are often typical reactions. A dose just short of a reaction gives the best final result.

Baerwolf (Berlin. klin. Woch., Nov. 14, 1921) deems it established that the suppuration in pyorrhea is not due to a specific microorganism, but that the various bacteria, streptococci, staphylococci, pneumococci and spirochetes play a part.

The treatment he advises calls, first of all, for removal of all local irritation in the mouth and restoration of vitality of the tissues. He treated 20 patients with Seitz's polyvalent vaccine, prepared from extracts of the freshly isolated organisms of different cases, and applied in ointment form. All deposits on the teeth must be removed before its application, otherwise severe gingivi-

tis arises. Before use of the vaccine, once daily, the mouth was washed with hydrogen dioxide, and alcohol diluted 1:10 applied at the gingivodental junction. The ointment was then introduced as deeply as possible with cotton swabs or a fine probe, and the gums gently massaged with it for 4 minutes. Definite improvement resulted in all instances.

### WRIGHT'S GENERAL PRINCIPLES OF THERAPEUTIC INOCULATION. IMMUNOTRANSFUSION.

Sir Almroth E. Wright, in collaboration with Colebrook and Storer (Lancet, Feb. 24, March 3 and 10, 1923), has reported on extensive researches into "new principles in therapeutic inoculations." In his review of the steps leading up to existing knowledge, Pasteur's original tenets are mentioned, followed by Wright's Code No. 2, which embodies the principles of vaccine therapy. Code No. 3 is founded upon a more detailed study of the changes produced in the blood by inoculation of vaccines *in vivo* and *in vitro*.

#### Code No. 1.—Original Pasteurian Code.

1. The essential preliminary to any prophylactic procedure is to possess ourselves of the pathogenetic organism, or, if this is as yet undiscovered, of the virus that contains it, and to manufacture a vaccine from this.

2. The vaccine must consist of living germs; but these must, with a view to the risk that would attach to the employment of virulent material, be attenuated.

3. When an appropriately attenuated vaccine, that is, a vaccine which can be warranted to produce only a moderate clinical reaction, has been obtained, the exact *quantum* implanted will not be of material importance.

4. Bacterial vaccines should be implanted subcutaneously.

5. Vaccination is applicable only to the uninfected.

6. The protection conferred by the vaccine is always specific; in other words, protection is obtained only against the species of pathogenetic agent of which the vaccine consists.

7. Protection is obtained only after the lapse of ten or more days from the date of inoculation.

The Pasteurian code did not consider anything but living attenuated organisms to be used for prophylaxis against infection. Protection for those already infected was not considered, excepting in the case of rabies where the period of incubation is prolonged. Wright supplements the code by the addition of:

8. Vaccination may be resorted to in the incubation period of a disease, provided that that incubation period has still more than ten days to run.

In the early researches by Wright, and Wright and Semple, on immunization against typhoid fever, it was shown that protective substances appear within 24 hours after vaccine is given, and that prophylactic treatment might be applicable to diseases with a comparatively short incubation period, the thought being to stimulate the production of protective substances by tissues of uninfected areas that are somewhat remote from the site of infection. From these observations Wright proposes his Code No. 2:—

1. The essential preliminary to all immunization procedures is to possess ourselves of the microbe of the disease or, failing that, of its virus, and to employ this as material for the manufacture of the vaccine. Here it may be parenthetically pointed out that inasmuch as in prophylactic inoculation the vaccines are stock vaccines and give good results, it cannot in any form of inoculation be theoretically essential to employ vaccines made directly from the patient.

2. Vaccines should, in all cases where the microbe can be cultivated outside the body, consist of sterilized cultures.

3. Vaccines may be turned to account in a variety of different ways. They may be employed not only for prophylaxis but also for preventive treatment in the incubation period of general infections. Again, they may be therapeutically employed in all localized infections other than those complicated by pyrexia and heavy and frequent autoinoculations. In this last class of infections, and also in those septicemic processes in which bacterial toxins in large quantity are circulating in the blood, vaccines are contraindicated.

4. Bacterial vaccines should be incorporated hypodermically.

5. The *quantum* of vaccine incorporated is of supreme importance; it affects both the kind of response and the rate at which protective substances appear. With only small doses of vaccine, or comparatively light autoinoculations, a positive phase or, as it may be better called, an *epiphylactic* or immunizing effect, may be registered in less than 24 hours after the incorporation of the vaccine. A similar but evanescent increase, known as the false rise, may be registered within a couple of hours after larger doses of vaccine and heavier autoinoculations. These larger inoculations of vaccine and heavier autoinoculations produce after that very fleeting positive phase a negative phase or—for these are better terms—an *apophylactic* or de-immunizing effect. And this effect is greater and lasts longer the larger the *quantum* of antigen carried into the blood.

6. In correspondence with the above the following rules of dosage may be laid down: In prophylactic operations undertaken in uninfected surroundings the dose should be that which evokes the optimum epiphylactic response, and it is for the attainment of that end permissible to employ doses which produce a temporary negative phase. When inoculating prophylactically in the presence of an epidemic, or in the incubation period of a general infection, and generally in the treatment of localized infections, reduced doses should be employed in order to avoid the constitutional disturbance and temporary aggravation of symptoms and dispersal of microbes in the organism. Re-



duced doses should also be employed where the chief matter of concern is to obtain with promptitude some clinical improvement.

7. The antibacterial substances elaborated in response to inoculation operate specifically upon the variety of microbe which has furnished the vaccine, but it is possible that in addition some collateral immunization is achieved.

The above code was Wright's basis for both prophylactic and therapeutic use of bacterial vaccines for many infections.

Code No. 3 further elaborates the two previous codes and introduces the principle of **immunotransfusion**. Experimental evidence is adduced to show that there is a strong basis for this code.

### Code No. 3.

1. While the nature of the infecting microbe should in every case be ascertained, it is not theoretically necessary that the vaccine employed in treatment or arrest of the incubating infection should be derived from the species of microbe which causes the disease. Sufficient justification for recourse to a particular vaccine is afforded when that vaccine has been shown to increase the antibacterial substances which operate upon the infecting microbe.

2. When vaccines in appropriate doses are added to the blood, whether *in vivo* or *in vitro*, instantaneous epiphyllactic response is evoked, and the maximal response may be expected after only very short delay.

3. The epiphyllactic response here in question consists in an extrusion of opsonic and bactericidal elements from the leucocytes. And it is mainly by the ectocytic chemical action, and only to an insignificant extent by phagocytosis and internal digestion, that the bactericidal action of the leucocytes is exerted.

4. The antibacterial substances here in question are polytropic—in other words, they operate not only upon homologous but also upon quite unrelated species of microbes.

5. Where the effective dose of vaccine for intravenous application has been ascertained, this method of administration is from considerations of certainty and rapidity

of therapeutic action to be preferred to subcutaneous inoculation.

6. In septicemias and other heavy bacterial infections the patient's leucocytes lose their power of responding to vaccines. In such cases it is essential before inoculating to satisfy one's self that the patient's blood still retains its power of epiphyllactic response.

7. Where, by reason of the poisoning of leucocytes, active immunization by means of vaccines is ruled out, the method of *immunotransfusion* should be resorted to—in other words, healthy human blood which has made proper epiphyllactic response should be incorporated.

The experimental observations were made with "slide cells," which consist of 2 sterilized slides, confining walls being provided for 4 compartments by the use of strips of paper  $\frac{1}{12}$  mm. thick dipped in very hot vaseline. These strips are placed on one slide, and the other slide laid on top of them. This device is used to measure bactericidal and phagocytic action.

The slides permit direct observation of bactericidal action, whether using whole blood, defibrinated blood, or serum with washed leucocytes. By this method Wright has shown that vaccines, *i.e.*, the soluble portions, acting as antigens, stimulate the production of bactericidal and opsonic substances in the blood. Again, when there is a response to these antigens the antibacterial elements are polytropic, as there is not only an increase in the homologous elements but also in those relating to other bacteria. There is thus given evidence of non-specific activity; hence the idea is conceived that there are common bactericidal elements and opsonins. In septicemias the bactericidal power seems to be little altered, but the response on the part of the leucocytes is decreased, so that no real protection is given from the

organisms which may be killed by the bactericidal serum.

When considering the possibilities of therapeutic inoculations one must also consider the type of infection. Mention is made of three types:—

1. Type of infection (exemplified by streptococcic endocarditis) with for a long time only very few microbes in the blood, with only moderate pyrexia, comparatively little constitutional disturbance, and a protracted and almost always fatal course. These cases would well be explained by assuming that the machinery of first defence has failed to do its office and that the epiphyllactic machinery has never been called into action.

2. The type of case (exemplified by croupous pneumonia) with from the outset an intense infection, high temperature, and heavy bacterial intoxication, and a course which very rapidly terminates either in death or in recovery by crisis. The cases which recover would be well explained by assuming that the epiphyllactic machinery is here effectively, though tardily, brought into operation; those cases which terminate fatally, by supposing the epiphyllactic machinery to have been put out of action by overwhelming bacterial intoxication.

3. The type of infection in which we have either a regular hectic temperature, as in phthisis and locked-up suppuration, or else such steep ascents and descents of temperature as accompany the rigors of acute streptococcus septicemias. Here one may assume—and such opsonic and bactericidal observations as are to hand are in accord with this—that whenever bacterial poisons in sufficiency are conveyed into or, as the case may be, generated in the blood, the machinery of epiphyllactic defence is, with results that are for the immediate moment satisfactory, called into action.

If immunity could in such cases be stimulated, advantage would be gained in three ways: First, the poisoning of the leucocytes—poisoning which upsets the machinery of both phagocytic and epiphyllactic defence—would be avoided. Secondly, the patient would be spared that intense systemic poisoning which

may bring him near to death before the life and death struggle with his infection even begins. And thirdly, the patient would be spared all that grave damage which is inflicted on his tissues at the site of infection.

In studying the production of bactericidal, opsonic, and phagocytic elements it was found that very small amounts of vaccine give very prompt and measurable amounts of these substances. Intravenous injections of such small numbers as 15 organisms per c.c. of circulating blood showed a definite increase in protective substances both in infected and normal individuals. An exceedingly important point is that the dose in a given case must be well chosen, since while a certain dose may increase the opsonic action of a serum, the phagocytic action of the leucocytes may be decreased or masked because of poisoning or exhaustion of the leucocytes.

From these experiments Wright believes that the slide cell method, the use of what he calls "emigration cells" and the capillary pipette are useful means for procedure, and that by following his technique, it is possible by one of these methods to determine whether a given patient is or is not able to respond to vaccine therapy. When it is determined that the patient will not respond, *immunotransfusions* may be considered. If such individuals can be given immune blood which is highly antibacterial and also assists the patient's leucocytes in resuming their normal functions, much good will result.

Wright records several cases in which such transfusions were given. Subsequently the patients did respond to vaccine therapy, whereas immediately before the transfusions their

blood had shown no ability to overcome the infection. The dose of vaccine given the prospective donor must be such as will not produce a negative phase, because the patient will not be benefited by such immuno-transfusions. Single intravenous inoculations were given the donors. In the experiments some time was permitted to elapse ( $\frac{1}{2}$  to 4 hours) between the giving of the intravenous inoculations and the time of transfusion.

This additional experimental work of Wright and his associates demonstrates that from bacterial vaccines properly given, with due consideration for dosage and the physical ability of the patient to respond, much good results. There is always a response to injections of bacterial vaccines. One must, however, have in mind the possibility of the negative phase in patients already burdened with toxins or circulating organisms. They must not be given doses that will lower their ability to produce immune bodies.

### BACTERIOPHAGIA.

Bacteriophagia may be defined as the activity of the bacteriophage. The suffix "phage" is not used in its strict sense of ingestion, but merely refers to the fact that the bacteriophage is propagated *at the expense of the bacteria, i.e., is, in a sense, parasitic.*

Hankin, in 1896, published a paper in the *Annales de l'Institut Pasteur* concerning the bactericidal action of a substance in the water of certain rivers in India. This antiseptic action was general as regards bacteria, but was in particular exerted against the cholera vibrio. In his experiments he filtered the river water through porcelain. One portion of the filtrate was used as it came from the filter; the other portion was boiled. Each portion was inoculated with a culture of the cholera vibrio. The plain filtrate became sterile, while the boiled filtrate showed an increase in the number of germs, yielding 36,000 at the end of 48 hours. Hankin,

as stated, believed that an antiseptic action had been exerted.

Twort, whose work appeared in the *Lancet* in 1915, made his observations in the course of some investigations with reference to the filtrable virus used in vaccination. He noted that certain colonies of a micrococcus became somewhat transparent and were replaced by fine granules. At other times, a film of transparent material was obtained; when this film spread, the micrococci were replaced by granules. The transparent vitreous substance, when diluted, would pass through a porcelain filter. It was active for at least six months, and was not destroyed at 52° C., although destroyed at 60° C. He obtained similar results from an organism of the colon group, isolated from the intestines of a dog, and another, not belonging in that group, but isolated from feces of an infant. The same vitreous substance transformed the normal culture. Twort believed it to be an enzyme which was destroyed at 60°. He propounded several hypotheses, but did not attempt to prove them.

D'Herelle, of the Institut Pasteur, Paris, whose labors, published in 1917, have brought the bacteriophage into prominence, and upon whose monograph, "The Bacteriophage," the present section is based, cites these two papers to draw a distinction between them. The observations of Twort he does not believe have to do with the bacteriophage, first, because the observations described cannot be reproduced by his bacteriophage, and second, because the bacteriophage of d'Herelle is not inactivated until a temperature of 75° is reached.

D'Herelle believes that the observations made in Haffkine's laboratory, where, at times, bouillon cultures of plague bacillus were found to become clear in a few hours, were due to bacteriophage. "I have had this experience in growing plague; in fact, it occurred so often that I discontinued using bouillon cultures. I believed, however, that it was due to some untoward action of certain lots of culture media."

The reports of Eliava's observations on the waters of the Kourg River were similar to those of Hankin. A few hours after inoculation of peptone water, cultures of cholera vibrio were obtained; later, the organisms could not be recovered.

Among the early interesting observations of d'Herelle was one concerning a patient with dysentery. *B. dysenteriae*, Shiga, was isolated. Each day a portion of the feces was cultured. After incubation over night, the culture was filtered and a portion of the filtrate was added to a culture of Shiga bacillus. This was repeated daily. One day it was noticed that no growth occurred. Upon inquiry it was found the patient was notably better. After further work, it seemed definitely established that the feces contained a principle which produced lysis of the dysentery bacilli. This was followed by the addition of the lysed culture, instead of the filtrate, to the culture, and it was found that this likewise dissolved the organisms. Further experimentation showed that this lytic activity had undergone an increase in potency.

It was further noted that upon addition of  $\frac{1}{100,000}$  c.c. of lysed culture to a young broth culture, followed by incubation for 1, 2 and 3 hours and the making of agar slants, the first tube showed 2 small areas, apparently without growth; the second tube, 6 such areas; the third, about 100, and the fourth no apparent growth at all.

The lytic substance appears, then, to multiply, and if it is a living cell, multiplies at the expense of the bacteria and belongs to the group of ultramicroscopic organisms.

When a trace of bacteriophage is introduced into a suspension of bacteria and lysis occurs, transfers may be made from this lysed culture to a fresh suspension, resulting in lysis of the new culture. This remains true indefinitely. In an instance in which 1500 transfers were made, the last tube was more active than the first, showing that there was a multiplication of the lytic substance.

**PREPARATION OF THE BACTERIOPHAGE.**—D'Herelle's method of demonstrating the presence of the germ in, and obtaining it from, liquid or semisolid material such as feces consists in suspending 2 to 5 Gm. of the material in 50 c.c. of bouillon. (The bouillon used must be alkaline, 6 c.c. of normal soda solution being added to 1 liter of neutral bouillon.) The mixture is incubated at 37° C. for 12 to 18 hours, then filtered through sterile paper and a sterile earthen filter, such as the Chamberland. Four tubes of peptone bouil-

lon having been inoculated from a 1-day agar slant culture of the dysentery bacillus or other bacterium, there is added to the 1st of these tubes 1 drop of the filtrate; to the 2d, 10 drops, and to the 3d, 2 c.c., the 4th serving as control. These tubes are incubated for 18 to 24 hours. Even if they are then cloudy, the bacteriophage may nevertheless be present. This is tested by spreading about 0.02 c.c. from each tube over agar slants with a platinum loop. If a normal growth of dysentery bacillus results upon incubation, the bacteriophage is absent; if it is present, the dysentery cultures on the agar slants will show a broken-up, moth-eaten appearance, with clear areas of no growth. Where 1 or more of the 3 original broth cultures had remained clear, this would in itself have shown the presence of the bacteriophage, the amount or virulence of it varying according to the results in the several tubes.

The bacteriolytic virulence of a bacteriophage not active enough to cause lysis in the original bouillon tubes is readily enhanced, as described by d'Herelle, as follows: The bouillon suspension is filtered through infusorial earth, then through a Chamberland bougie. A slightly cloudy bouillon suspension of the bacterium in question (*e.g.*, the dysentery bacillus) is prepared, 4 or 5 drops of the filtrate added, and the suspension incubated for 24 hours. If lysis has not occurred, this 2d suspension is filtered as before and the process repeated. The rising bacteriolytic power of the bacteriophage can be followed by observing the results in subcultures on agar slants. After a few repetitions, bacteriophagic virulence is so enhanced that lysis of the bouillon bacterial culture occurs when the few drops of filtrate are added to it and it is incubated.

The bacteriophage may also be increased in virulence in the peritoneum of the guinea-pig: Inject 2 c.c. of fluid containing the bacteriophage and the culture against which it is active. After 12 to 18 hours, inject 10 c.c. of broth; after a few minutes remove the fluid and filter through a porcelain filter; then test for activity.

The bacteriophage may be cultured on agar by transplants from the cleared areas in a tube which has shown both bacteria and bacteriophage. By successive trans-

plants, a point is reached where no organisms are shown. At this point the bacteriophage may be washed off, filtered as in the mode of production previously discussed, whereupon the filtrate will contain this ultramicroscopic material which produces lysis in bouillon cultures of the organism.

D'Herelle also describes a procedure for counting the number of bacteriophages in any given filtrate. It is based on the number of clear spaces observed in bacterial cultures on agar slants, each clear space, under suitable dilution, being taken to represent a single unit of the bacteriophage. The method is thus similar to that customarily followed in counting bacteria. By this procedure, such figures as  $2\frac{1}{2}$  or 3 billion bacteriophages per c.c. of the original filtrate are obtained.

A further step worked out by d'Herelle consists in so diluting a bacteriophage culture that only a single bacteriophage may be inoculated in a bacterial bouillon culture. For example, a culture containing 3 billion bacteriophages per c.c. is so diluted that but 1 six-billionth of a c.c. of it is added to each of a series of bacterial cultures. In such an experiment, 4 out of 6 dysentery bacillus cultures developed normally—including agar slants—indicating that not a single bacteriophage had entered them with the minute amount of filtrate added. In the other 2 tubes, each receiving 1 or possibly 2 bacteriophages, the suspension showed increasing turbidity up to 4 hours, then a gradual clearing in the succeeding 10 hours. From the 5th hour on, subcultures on agar slants were negative, and at that hour the suspension was calculated to contain already  $1\frac{1}{2}$  million bacteriophages. This points to an extremely rapid rate of reproduction; furthermore, the multiplication of the bacteriophage seems to take place by successive starts, at intervals of about 75 minutes.

D'Herelle states that the bacteriophage is an obligate parasite, its multiplication occurring only at the expense of living bacteria. In his experiments on this point, he found that a bacteriophage will not grow and multiply where the organism has been treated by some antiseptic. Apparently the bacteriophage is more sensitive to antiseptics than are bacteria themselves.

The nature of the culture medium has

little influence, except that the medium must be alkaline and contain no glucose, because of the acid production which occurs in media containing this substance. For this reason peptone containing even small amounts of glucose cannot be used in this work.

The bacteriophage grows in circular plaques. If sufficiently heavy, a continuous growth appears instead of the separate plaques. No growth of bacteria against which the bacteriophage is active occurs in these colonies. That these plaques consist of active material is shown in that if a loop of the plaque is transferred to a culture of Shiga bacillus, it will develop in the culture, which will undergo lysis in a few hours.

The bacteriophage is facultative, growth occurring either under aërobic or anaërobic conditions. Temperature, however, has an appreciable affect. Between  $37^{\circ}$  and  $41^{\circ}$  C. there is no appreciable difference, but above this temperature, growth is less active. The organism can still be cultivated at  $44^{\circ}$  C.

That the bacteriophage acts in the nature of a parasite is shown in that after 30 minutes' contact with bacteria against which it is active, at  $37\frac{1}{2}^{\circ}$  C., most of the ultramicrobes will have disappeared from the fluid. After  $1\frac{1}{2}$  hours, however, there is an increase in the number of the ultramicrobes present. From this it would appear that the bacteria act as hosts, the ultramicrobes gradually multiply, and finally the bacteria undergo lysis, with release of the ultramicrobic bodies. If smears are made of the culture at intervals and these are stained, it will be found that after 30 minutes a few of the bacilli stain poorly; between 1 and 2 hours the number that stain poorly continues to increase, and after 2 hours, very few stain normally. Débris and granulations appear. Gradually some spheroidal forms make their appearance, varying considerably in size; occasional long bacillary forms are seen, and then finally these forms disappear. After four hours, only here and there can a bacillus be seen, poorly stained. The débris gradually disappear and finally the granules, and after 36 hours, nothing whatever is visible in these preparations.

This same process is seen under the ultramicroscope. The bacillary forms gradually

diminish, granules appear within the cells, spheroidal forms are seen, and actual bursting of these forms can be observed. It would seem that this bursting force must come from within, since this period corresponds to the time at which the bacteriophage is greatly increased in numbers; also that the granules represent the bacteriophage elements. If this process were due to a ferment, then the action would proceed along in a definite manner; but each lot of bacteriophage acts differently as to time, according to its virulence, although the ultimate results are always the same.

Another feature is the resistance of organisms to the action of the bacteriophage. It has been noted that cultures which had been subjected to the action of this ultramicrobe and had been apparently lysed, developed a turbidity after 5 or 6 days, which turbidity was shown to be due to the strain of organism used in making the suspension. Experimental evidence shows that the bacteria under such circumstances have acquired a power to resist the action of the bacteriophage, and that their presence is not due to lowered virulence of the latter.

The equilibrium of these factors can be disturbed in certain ways. Thus, the activity of the bacteriophage can be unfavorably influenced by an acid medium; or, the resistant forms of the bacteria can be modified by the use of a 3 per cent. glycerine bouillon so that greater activity of the bacteriophage is in evidence.

Not infrequently, when an active bacteriophage and bacteria are brought together, agglutinated masses are seen. These agglutinated bacilli become the resistant forms. There are at times what appear to be two different organisms, when they are studied in their colony formation. This is apparently due to the bacilli having assumed the resistant form. The resistant forms may take on a coccoid shape, or they may develop a mucoid consistency. When the coccoid form has developed, a number of transplantations are required before the germs return to their normal morphology and become again subject to the activity of the bacteriophage.

These coccoid forms are not agglutinable by specific serum. When they are injected into a rabbit, paralysis and intestinal lesions are observed. When sublethal doses are

administered to animals, the latter develop an immunity against the typical, normal organisms.

This phenomenon of organisms resistant to agglutinating serum has been noted many times in the case of freshly isolated typhoid bacilli, which, after a number of transplantations on agar, become agglutinable; d'Herelle states that this is due to the resistant type of organisms developing as a result of the presence of the bacteriophage in the intestinal tract. It would appear, from some of the work, that some of the bacilli actually carry the ultramicrobes, for when a bacteriophage of low virulence is inoculated into a heavy suspension, the bacteriophage disappears or apparently so. But later on, after several platings, the bacteriophage may suddenly appear in a colony. This, when transplanted, continues to grow by itself and, after a number of transplantations, yields plaques of very considerable activity. Hence the assumption that the bacteria have actually been carriers of the bacteriophage, the bacteriophage from some of these experiments producing a very active lysin. If the ultramicrobes have very high virulence and are inoculated into a heavy suspension, the bacteria appear to have had time to adapt themselves and neutralize the lysin produced, and it has been shown that the antilynsins are specific in that they are devoid of inhibiting action for the lysis produced by bacteriophage specific to other bacteria.

When freshly isolated, the bacteriophage seems to be able to attack more than one species. It may be highly active against *B. dysenteriae* and less so for *B. coli*, *B. typhosus* and *paratyphosus*. Complement-fixation tests seem to demonstrate that there is but one form of bacteriophage.

The bacteriophage active against *Staphylococcus aureus* isolated by Eliava from the pus of an abscess was, after a number of transplantations, active against *B. dysenteriae*. After the bacteriophage had been followed as parasite to *B. dysenteriae* through a number of generations, it became inactive for staphylococcus and could not again be made to assume its earlier relationship to that organism. So far it has not been possible to reverse this order, i.e., to have a dysentery bacteriophage become active against staphylococcus.

The bacteriophage may be preserved either in the original material or in filtrates. It may during this time, however, lose some of its virulence for certain organisms against which it had been active, retaining its virulence against others.

The following strains of bacteriophage have been demonstrated:—

A strain active against *B. dysenteriae*, Shiga, is often normally present in the intestinal tract of animals, including the horse and domestic fowls. This strain is equally active for the Flexner and Hiss strains, and also for *B. coli*.

A strain active against *B. typhosus* can frequently be isolated from the normal intestines. Very active cultures are found only in convalescents from typhoid fever.

An active strain against *B. paratyphosus* A and B and *Salmonella* (hog cholera) have been isolated from normal stools.

A strain against *B. typhi murium* has been obtained from the intestinal tract of white and gray rats after feeding them cultures of the organism.

Strains for *B. proteus* have been isolated from the intestinal tract of infants suffering with gastroenteritis.

Strains have also been isolated which are active against *B. gallinarum*, diphtheria, staphylococcus, hemorrhagic septicemia of the water buffalo, *B. pestis*, a disease of silkworms, and cholera.

The bacteriophage is able to pass through dialytic membranes that allow albumin to pass; where albumin is held back the bacteriophage is likewise held back. Its resisting powers are very great. Filtrates and cultures containing it have proven active after preservation for six years in a sealed tube. It is relatively resistant to mercuric chloride, copper sulphate and phenol, but is destroyed after a number of days by these chemicals. In 50 per cent. glycerin it remains alive for at least two years. It is killed by 3 per cent. quinine solution, emetine hydrochloride, acetone and alcohol. In the latter, it is killed in somewhat less than 48 hours.

D'Herelle has been able to study the bacteriophage in relation to bacillary dysentery, typhoid fever, paratyphoid fever, the typhoid of fowls, and the septicemia of water buffaloes. He is convinced that there is but a single species of bacteriophage. It

is, however, capable of adaptation, assuming virulence for different bacteria which it may attack. He terms it *Bacteriophagum intestinale*. It has been recovered from all human organs, though found chiefly in the alimentary tract. It has also been found in the urine, the blood, effusions, river and sea water, and in the soil, seeming, in fact, practically ubiquitous.

The bacteriophage in the intestinal tract of normal persons may be inactive against many organisms, but if tests are carried out with a sufficient number of bacteria, in all probability there will be found some against which it is active. Even when this cannot be demonstrated, he believes the organism to be present, its activity being called forth by infection.

As a normal inhabitant of the intestine, the bacteriophage lives therein at the expense of the saprophytic bacteria, which have an inherited partial resistance to it. When a new bacterial invader enters the bowel, the virulence of the bacteriophage against it becomes heightened and may, in the absence of an acid reaction or of a bacteriophage-resistant property already acquired by the invader elsewhere, overcome the invader and prevent development of disease in the host. Where disease does develop, convalescence sets in only when the bacteriophage finally gets the upper hand over the bacteria. In germ carriers, a state of balance or commensalism (as in the normal intestine) is regarded as having been established between the bacteria and the bacteriophage. When injected subcutaneously, the bacteriophage soon reaches the intestine, as shown by tests, while in septicemias it can enter the blood from the bowel and exert its effect at any point in the body. The lysins of the bacteriophage possess an extremely high opsonic power. Bacteria resistant to the bacteriophage are simultaneously resistant to phagocytosis.

D'Herelle regards the bacteriophage as playing a preponderant rôle in the defence of non-immune individuals exposed to infection or already suffering from disease, whereas the phagocytes eliminate bacteria when immunity is already established.

Successful immunization experiments were carried out by D'Herelle in avian typhoid. Cultures of active organisms were inoculated with the bacteriophage active against

the particular organism. When lysis of the bacteria was completed, the material was filtered and then kept in ampules for inoculations. Injection of this material produced definite results. In each case, an epidemic was immediately controlled when the epidemic was due to organisms against which the bacteriophage was active.

Immunization experiments were also carried out among cattle in non-infected areas. A very definite immunity was established. Passive immunity was produced with the bacteriophage of the septicemia of the water buffalo by inoculating animals with the serum of immunized animals. Injection of water buffalo or cattle with an active culture of bacteriophage induced heterologous and homologous immunity. Heterologous immunity is usually quickly lost. Homologous immunity, however, is extremely active, and d'Herelle is inclined to look upon it as the result of an antitoxin. This immunity is established within 4 days by so small a dose as 0.04 c.c. per 100 kgs., at which time the animals withstand 5 fatal doses. In 60 days they can withstand 50 fatal doses.

Immunization experiments were likewise performed successfully in rabbits with cultures of Shiga lysed by the ultramicrobe.

**THERAPEUTICS.**—The property of the bacteriophage of destroying bacteria has led a number of observers to investigate its possible utility in the treatment of disease. D'Herelle reported 5 cases of Shiga bacillus **dysentery** in children in which ingestion of bacteriophage cultures was the only treatment given. All had bloody stools, ranging from 5 to an uncountable number daily. All were cured bacteriologically and clinically in 9 to 14 days.

Successful use of the bacteriophage by subcutaneous injections in **staphylococcal infections** was reported by R. Bruynoghe and J. Maisin (C. r. Soc. de biol., lxxxv, 1120, 1921). A. Beckerich and P. Hauduroy (*Ibid.*, lxxxvi, 168, 1922) reported 5 cases of **typhoid fever** and 2 of **paratyphoid B** treated with the bacteriophage by injection of 2 c.c. and in 3 instances also by injection of 1 c.c. In all, permanent defervescence occurred within 48 hours, though 2 cases died, possibly because of pronounced myocarditis or insufficient dosage.

A sweat occurred 2 hours after the treatment. Two cases of **pyelocystitis** due to *B. coli* were also treated by injection of 1 c.c. of the corresponding bacteriophage, with permanent defervescence in 48 hours. In a case of **pyelonephritis** in pregnancy, Courcoux, Philibert and Cordey (Bull. Soc. méd. des hôp. de Paris, July 21, 1922) used the colon bacillus bacteriophage subcutaneously and also injected 15 c.c. into the bladder. After a distinct reaction for 48 hours, recovery promptly took place. W. C. Davison (Amer. Jour. Dis. of Childr., June, 1922) observed no definite results from the bacteriophage in 12 cases of bacillary dysentery, possibly because in most instances the treatment was begun late. The only 2 cases treated within the 1st week recovered.

In 11 cases of colon bacillus **pyelitis** or **cystitis**, Beckerich and Hauduroy (Bull. méd., Mar. 10, 1923) injected a bacteriophage preparation obtained from cases of puerperal pyelocystitis. In 6 cases the colon bacillus infection was rapidly and completely cured, and in 1, clinically cured. Cases in which the colon bacilli seem to resist the lytic action of the bacteriophage are not suitable for the treatment.

A. Alessandrini and R. Doria (Policlin., Jan. 28, 1924) prepared from the feces of a typhoid patient at the beginning of defervescence a polyvalent bacteriophage yielding complete lysis of 5 typhoid strains in 6 to 8 hours. This preparation retained its activity undiminished for months. The writers used it in 18 cases of **typhoid fever**, giving it by mouth, with or without subcutaneous, intramuscular or intravenous injection. It was always well borne, though doses of 2 to 4 c.c. subcutaneously or intramuscularly caused a transient local reaction, and intravenous injection caused colloidoclastic shock in 3 out of 4 cases. By either route it caused a transient rise of temperature. In  $\frac{1}{2}$  the cases the course of the disease was shortened, the temperature reaching normal in 6 to 8 days, at whatever stage of the disease the remedy was used. Results were best in the cases in which the individual typhoid strain present showed itself most susceptible to the lytic effect.

D. Herderschee and L. K. Wolff (Nederl. Tijds. voor Geneesk., June 14, 1924) have



also used the bacteriophage in **typhoid fever**, and deem it of definite, though not specific, utility. Of 105 cases receiving the treatment in an epidemic, 15 died, as against 20 deaths among 95 cases not receiving it. They prefer this treatment to the injection of killed typhoid bacilli. They use a mixture in equal parts of 2 bacteriophages which, according to d'Herelle, antagonize all known strains of the typhoid germ. Recovery occurred very rapidly under the treatment. Usually 2 injections were given at an interval of 2 or 3 days.

As the bacteria react to the lysin by the formation of antilyns, which impede the therapeutic action, the 1st injection of the bacteriophage is much more active than later ones, according to K. Marcuse (Deut. Med. Woch., Mar. 14, 1924). Parenteral injections vary in efficacy according to the accessibility of the seat of infection to the lysin. Thus, the best procedure is, if possible, to apply the bacteriophage locally to the affected area. This the writer did in experimental colon bacillus cystitis in guinea-pigs. When 0.2 c.c. of active lysin was twice introduced directly into the bladder, the urine cleared up completely in 9 days, while still showing an abundance of colon bacilli in the control animals.

A bacteriophage filtrate showing marked polyvalence to colon and dysentery bacillus strains has been prepared by E. Zdansky (Wien. klin. Woch., May 15, 1924) from sewage. Twenty-eight different strains of colon bacillus were dissolved completely, with 1 exception, by this filtrate.

E. B. McKinley (Arch. of Int. Med., Dec., 1923), in a variety of cases, administered the bacteriophage subcutaneously, by duodenal tube, into wounds, on dressings, by ureteral catheter, intranasally, intra-aurally or by mouth in amounts ranging from 1 to 50 c.c., with encouraging results. It proved harmless even in the larger doses. (Davison in 1 case gave 1300 c.c. without bad effect.) The bacteriophages, obtained from various sources, were enhanced in virulence by d'Herelle's method [see preceding section of this article] until sterile agar subcultures were obtained. The filtrate—usually 30 to 50 c.c.—was then allowed to dissolve bacteria in increasing numbers on 5 successive days up to a total of 30 billion bacteria, this process affording

a species of standardization of the bacteriophage. The filtrate remaining clear, further filtration was nevertheless carried out as a precaution and the filtrate incubated for 24 hours to prove its sterility before clinical use.

In 4 cases of **chronic suppurating wounds**—3 following removal of a piece of bone in **compound fracture**—injections of 1 to 3 c.c. of bacteriophage into the wounds were followed by cessation of the profuse discharge and prompt healing. Usually the 1st injection led to an abrupt reduction of discharge within 24 hours; altogether 3 to 6 injections were made. In a case of staphylococcal **pyelitis** following removal of a kidney stone, 4 injections, each of 8 c.c. of bacteriophage, into the renal pelvis through the ureteral catheter at 3-day intervals were followed by a rapid clearing up of the condition. In a case of streptococcal **abscess of the lung** with profuse, foul discharge following rib resection and drainage, the odor and discharge practically ceased in 2 days after injection of 30 c.c. of bacteriophage into the cavity, and after 2 further injections at 3-day intervals the wound healed and the patient was discharged 8 days after the 1st injection. In a case of **chronic dysentery** of 9 years' standing showing the Flexner dysentery bacillus, administration of 30 c.c. of bacteriophage through the duodenal tube on 2 occasions, 1 week apart, relieved the symptoms in a few days, and the patient was quite well for over 2 months. In 2 cases of **chronic maxillary sinusitis**, intranasal use of bacteriophage cultures from sterile atomizers was followed by profuse discharge for 1 day, then absence of discharge for 10 to 14 days, after which the discharge recurred. In a case of **chronic otitis media** with discharge, originating in scarlet fever many years before, introduction of the bacteriophage into the ear in 1-c.c. amounts was followed by complete subsidence of the discharge. In 3 cases with a clinical diagnosis of **subacute catarrhal cholecystitis**, use of a stock bacteriophage by duodenal tube in amounts of 15 to 50 c.c. was followed by complete relief of symptoms for 2 to 3 months, after which the symptoms returned in a milder form.

In 20 positive cases of **bacillary dysentery**, R. C. Spence and E. B. McKinley

(South. Med. Jour., Aug., 1924) started giving 10-c.c. doses of bacteriophage—previously put up in ampoules—by mouth 3 times daily immediately on admission. The mortality in these cases was 10 per cent., and the 18 survivors were symptom-free on an average 5.8 days after beginning of treatment, while in 12 control cases the mortality was 40 per cent. and the symptoms disappeared 12.8 days after the beginning of hospital treatment.

N. W. Larkum (Abst. of Bact., Aug., 1925) made a study of urinary tract infections due to *B. coli*, in order to determine the possibility of therapy with the bacteriophage in such diseases. Urines from infected individuals often contained bacteriophage, while normal urines were always free of it. Bacteria susceptible to lysis with the bacteriophage were present in about 40 per cent. of the individuals studied. In the acute stages, the bacterium was practically always susceptible to lysis. As to the mode of administration, bladder and kidney instillations were found to be most advisable. Three cases responded to treatment very well and were free from symptoms and organisms within 10 days from the beginning of treatment.

The technical procedure is as follows: A specimen of urine from the patient is cultured in alkaline extract broth, pH 7.8. After isolation of a single colony, agar slants are streaked, and after eighteen hours the growth is washed off with about 10 c.c. of broth. Tubes containing 10 c.c. of alkaline extract broth are then inoculated with a drop of the suspension. As many tubes are inoculated as there are races of bacteriophage available plus one which serves as control. The one race of bacteriophage used by the writer showed a relatively wide range of virulences. After incubation of the bacterium-bacteriophage mixture lysis is seldom visible; hence, the tube contents is filtered. The sterile filtrate is then added to a fresh suspension of the organism, and the process repeated. Usually, if no evidence of lysis is present after 5 or 6 contacts the writer desists, although occasionally he has succeeded after 10 or 12 contacts. A race of bacteriophage effective in all cases may eventually be found, but at present each case must receive individual attention and be the sub-

ject of considerable laboratory work unless the first contact shows a susceptible bacterium. Having the necessary conditions—susceptible bacterium and virulent bacteriophage—5 to 10 c.c. of bacteriophage in 20 c.c. of saline are instilled into the bladder. At the same time 0.2 c.c. of the principle are injected subcutaneously. This is repeated 24 hours after the first treatment, then discontinued. There are reasons, chief among which is the possibility of the development of an antibacteriophagic antibody, why the treatment should not go on. Apparently, if a cure is to be effected by this means, 2 treatments are as effective as 20.

Bronfenbrenner and Korb (Jour. of Exp. Med., Dec., 1925) have observed no persistent differences in the individual resistance of lytic filtrates active against different micro-organisms in ways that lead them to favor the conception of a multiplicity of bacteriophages.

A. PARKER HITCHENS,  
Manila,  
AND  
CLAUDE P. BROWN,  
Philadelphia.

**BACTERIURIA.**—If freshly voided urine free from pus is turbid, the turbidity being due entirely to the presence of micro-organisms and not to urinary salts, this condition is referred to as "bacteriuria." In giving this definition, L. E. Schmidt (Ill. Med. Jour., xxxvi, 188, 1919) states that there is a class of cases of bacteriuria in which pus is found in the urine because of the presence of an inflammatory condition. In the vast majority of cases seen in routine practice the urine contains pus in varying amounts and this pus may or may not have a bearing on the bacteriuria.

In the *colon-bacillus* infections of the kidneys, pus and blood are found in the urine as well as large numbers of bacteria. In some other conditions also, the bacteria may descend from the upper urinary tract but the pus may come from some chronic inflammatory condition of the urethra or adnexa.

Another class of cases are those in which the presence of pathologic conditions outside of the urinary tract has been definitely

demonstrated and the bacteria, pus, and blood make their entrance into the urinary stream from these foci. There is likewise a group in which there is a complete absence of demonstrable lesions and pus, and the turbidity of the urine is due entirely to the presence of bacteria.

It is highly desirable to ascertain where the bacteria enter the urinary stream. In the acute infectious diseases, such as *typhoid fever*, it is not at all uncommon to find the true bacteriuria due entirely to the *Bacillus typhosus*, pus and blood being absent. Again, in chronic *pulmonary tuberculosis*, investigations have shown that in a fair percentage of cases the *Bacillus tuberculosis* is eliminated through the kidneys constantly. The same is true in many other infectious diseases. At any time the bacteria may cause an inflammatory disease of the urinary tract which may be the only involvement or may be concomitant with the bacteriuria. Occasionally bacteriuria has been noticed following *instrumental treatment* or examination and therefore it has been concluded that the point of entrance was an injury.

Bacteria are pathogenic at certain times and non-pathogenic at others, and sometimes cause marked inflammatory reaction and at others are apparently not injurious to the same tissue. The *colon bacillus* may, for example, cause most violent attacks of true infection of the kidneys, high temperature, chills, and most pronounced general and local signs and symptoms.

The symptoms of bacteriuria vary. In some patients local and general symptoms are practically absent while in others there may be headache, backache, a feeling of extreme fatigue, and perhaps a rise in temperature and chills. Others, again, show only local urinary symptoms, or both general and local symptoms.

Systemic and local treatment, including **vaccines**, is helpful. Nolf (N. Y. Med. Jour., Dec. 20, 1919) found progressive **intravenous vaccination** very satisfactory.

**BARBITAL.** See VERONAL.

**BARIUM.**—The metal barium, which is not used medicinally, occurs in nature as a sulphate termed barite, and as a carbonate: witherite.

## PREPARATIONS AND DOSE.

—The only salt of barium used to any extent in therapeutics is the chloride, *barii chloridum*, a white, crystalline salt having a bitter, disagreeable taste. The *dose* is  $\frac{1}{10}$  to 1 grain (0.006 to 0.06 Gm.). Some have advocated smaller doses, *viz.*,  $\frac{1}{40}$  to  $\frac{1}{10}$  grain (0.0015 to 0.006 Gm.). It is readily soluble in water and fairly so in alcohol. It is not official.

Barium sulphate was made official in U. S. P. X (1926) as *Barii sulphas*. It is insoluble in water and is used for diagnostic purposes only.

## PHYSIOLOGICAL ACTION.—

The main action of barium is on the cardiovascular system. It increases, as does digitalis, the power of the cardiac contractions, but reduces their number. It enhances also the tonicity of the blood-vessels, causing an increase of the vascular tension. The tracings of barium and digitalis are strikingly alike.

It presents the peculiarity of being able to restore the contractions of the heart when these have been arrested by muscarine or chloral. Large doses first stimulate the heart's action, but this is soon converted into depression, with irregularity, weakness, and later on imperceptibility of the pulse. The blood-pressure is influenced in the same way, a rise being soon succeeded by a more or less sudden fall, according to the dose administered. As has been shown by Meyer, barium passes out mainly with the feces.

**BARIUM POISONING.**—Excessive or toxic doses tend to give rise to symptoms of cardiovascular failure, the pulse being weak, slow, and irregular. Besides these effects, however, there appear phenomena due to violent excitation of the gastrointestinal

musculature, *viz.*, vomiting and diarrhea, soon followed by intense weakness, dyspnea, hypothermia, albuminuria, hemoglobinuria, and, the latter increasing gradually until asphyxia is approached, death following after a few clonic convulsions. In either favorable or fatal cases paresis or paralysis may be noted. The muscles of speech early become very weak, but consciousness is retained to the end. After death, which has been attributed to the formation of multiple emboli, there is early rigidity, with lesions in most organs, particularly in the kidneys, in which tubular hemorrhages are frequent, with granulofatty infiltration of the secretory epithelium.

Owing to the toxic symptoms which sometimes occur after taking large doses of bismuth mucilage in *X-ray examinations*, a perfectly harmless substitute for bismuth had been sought. **Barium sulphate** has been advised and adopted for this purpose; it is insoluble in water and in acids, and trials made on man have demonstrated its harmlessness, as it passes through the stomach and intestines unchanged, and there is no unpleasant action whatever. Only a pure product should be employed, however. It must be absolutely free from soluble salts of barium, the presence of which, even in small quantities, produces toxic effects. Great care should be taken *not to use the barium chloride or the barium carbonate*, which becomes converted in the stomach into the former very poisonous salt.

**TREATMENT OF BARIUM POISONING.**—This consists in administering **magnesium sulphate** or **sodium sulphate** in white of egg, after administering an **emetic** or carrying out **stomach lavage** if there is reason to believe that any of the poison is still in the stomach. As barium chloride is absorbed slowly from the intestine, it is also advisable

to administer a **saline purgative**. **Heat and stimulating measures**, *e.g.*, **aromatic spirit of ammonia** and **strychnine**, are important adjuncts.

Bardet reported a case in which  $2\frac{1}{2}$  grains (0.016 Gm.) in divided doses sufficed to cause death, while of 2 other cases mentioned in the dispensatory 1 case survived after taking 60 grains (4 Gm.), and the other died after taking 300 grains (20 Gm.). Phillips states that, while the minimum fatal dose is commonly put at 1 dram (4 Gm.), this dose has caused death in seventeen hours.

In a review of the literature from 1910, the writer found 12 deaths from barium carbonate, 6 from barium chloride, and 4 from barium sulphide. He adds 2 cases. In one, a man took 4 ounces of barium carbonate in a pint of milk, a physician having prescribed this salt by mistake in place of the sulphate. Vomiting occurred in a few minutes, but no antidotes were given, the cause of the illness not being realized. Death took place in  $8\frac{3}{4}$  hours. In the other case, a woman took 2 ounces of barium sulphide in  $\frac{1}{2}$  pint of buttermilk, dispensed in error. She died in 3 hours. W. D. McNally (Jour. Amer. Med. Assoc., June 13, 1925).

**THERAPEUTICS.**—Da Costa held that barium was advantageous in cardiac disorders, including **valvular diseases** in which digitalis was indicated; he found that it reduced the cardiac distress and increased vascular tone and diuresis, while, moreover, it could be administered a long time without disordering the stomach. While digitalis is superior to barium in every respect, the latter has been recommended at times for the milder degrees of **cardiac insufficiency**, especially with low blood-pressure. This applies also to failure of the circulation in acute diseases, **pneumonia** for

example. Phillips spoke favorably of barium chloride in **mitral disease** and **cardiac dropsy**, but in very small doses,  $\frac{1}{40}$  grain (0.0015 Gm.) three times daily. Hare and Carpenter also favor its use, the latter advocating 30 minims (2 Gm.) of a 1 per cent. solution, gradually increased to 2 drams (8 Gm.). Cohn has reported 3 cases of **Adams-Stokes disease** which seemed definitely benefited after digitalis had failed.

McCall Anderson has employed the barium sulphide for the removal of **surplus hair**, "one part being made into a paste with four parts of zinc oxide and a little water; this should be left on the part for about three minutes and then washed off. It should be prepared only as required for use" (Phillips). Barium chloride has been claimed useful in **chlorosis**, especially when the blood-pressure is low.

C. E. DE M. SAJOUS,  
Philadelphia.

**BASAL METABOLISM.**—The basal metabolism or basal metabolic rate refers to the minimal heat production of the body, measured 12 to 18 hours after ingestion of food (post-absorption state) and with the body at complete rest in a comfortably warm environment. The amount of heat produced is taken as an indication of the level of vital activity, and while heat is the natural result of the oxidative processes constituting a large portion of all tissue activity, the metabolic rate can be determined not only by *direct* measurement of the heat thrown off, but also *indirectly* by measurement of the oxygen intake, the CO<sub>2</sub> output, or both.

**APPARATUS AND TECHNIC.**—Direct calorimetry, requiring the use of a complicated and expensive respiration calorimeter chamber, is availed of only in a few specially equipped institutions, and is ordinarily replaced by indirect calorimetry, of which 2 varieties exist. The 1st

is known as the *open circuit method*: The expired air from the patient is received in a spirometer bell or bag, from which samples are then removed for determination of the oxygen and CO<sub>2</sub> content. This method is time-consuming and calls for relatively complicated gas analyses. The procedure generally adopted, therefore, is the *closed circuit method*, in which the patient breathes out of and into a spirometer bell containing oxygen, the gradual descent of the bell as the oxygen in it is consumed affording the required data for metabolic rate determination. The respiration of oxygen instead of air does not vitiate the results, it being a known fact that when oxygen is breathed the amount of oxygen taken up by the blood and used in the tissues is the same as when ordinary air is inspired. This circumstance permits the use of a spirometer bell much smaller than would be required if air were breathed instead of oxygen.

The recent closed circuit forms of *apparatus* are practically identical in principle, and the following description of the Roth-Benedict apparatus, condensed from H. F. Moore (Lancet, Jan. 31, 1925), will suffice for general guidance: The cylindrical spirometer bell is suspended by a pulley over a double-walled cylinder closed below and filled with water. In the inner space is a chamber filled with soda-lime (to absorb the CO<sub>2</sub>) connected through rubber tubing with the mouthpiece in the patient's mouth. There is also another outlet from the oxygen chamber, with tubing leading to the mouthpiece. In this tubing is a valve which closes on expiration, while over the soda-lime chamber is a valve which closes on inspiration. Thus, when the patient breathes out, the expired gas passes through the soda-lime (which removes the CO<sub>2</sub>), and when he breathes in, he receives pure oxygen from the bell. The cord over the pulley carries a counterpoise weight, to which is fastened a pointer with pen attached, the latter writing on a revolving drum, upon which a suitable time-marker also registers. As the bell falls and rises with each respiration, corresponding up and down strokes are recorded on the drum; but the tracing as a whole also gradually rises because of the progressive exhaustion of the oxygen in

the bell, thus affording a record of the oxygen consumption in any given period.

Corrections are made in the reading for temperature, barometric pressure and relative humidity.

The calculation is based on the assumption that 1 liter of oxygen absorbed by the patient corresponds to 4.825 calories set free (this being based, in turn, on 0.82 as the average respiratory quotient). To shorten the calculation as much as possible, with the Roth apparatus a 6-minute ( $\frac{1}{10}$  hour) section of the tracing is used and the bell is constructed with a volume of 20.73 c.c. per mm. of its height. Thus, each millimeter of fall of the bell or rise of the tracing in the 6-minute period corresponds to 1 calorie per hour (since  $0.2073 \times 4.825 = 1$ ). If the tracing has risen 78 mm. in the 6 minutes, the liberation of calories per hour by the patient is 78. The temperature correction is made by comparison of the spirometer temperatures at the beginning and end of the test (the spirometer bearing a thermometer at its upper end). If a rise exceeding  $1^{\circ}$  C. has occurred, 0.5 mm. is added to the total rise of the tracing for each degree of temperature rise.

The corrections for barometric pressure and humidity are made by multiplying by a factor obtained from a table.

Further mathematical manipulation of the result is required in order to obtain a figure comparable in all individuals and a basis for expression of the metabolic rate as a definite percentage above or below the normal. Rubner having suggested that the heat production of an individual is proportional to his surface area, D. Du Bois devised a simplified formula by means of which the surface area can be deduced with reasonable accuracy from the individual's weight and height. Thus:

$$\text{Surface area} = W^{0.425} \times H^{0.725} \times 71.84$$

(W = weight in kilograms;

H = height in centimeters).

On the basis of this formula Du Bois has constructed a height-weight chart by means of which the surface area can be estimated at a glance. The Aub-Du Bois standards of normal basal metabolism for age and sex are regarded by Booby and Sandiford as the best now available, and are as follows:

AUB-DU BOIS STANDARDS.  
Cal. per sq. meter of body surface per hour.

Age	Males.	Females.
8 to 9	54.0	54.0
10 to 11	51.5	50.0
12 to 13	50.0	46.5
14 to 15	46.0	43.0
16 to 17	43.0	40.0
18 to 19	41.0	38.0
20 to 29	39.5	37.0
30 to 39	39.5	36.5
40 to 49	38.5	36.0
50 to 59	37.5	35.0
60 to 69	36.5	34.0
70 to 80	35.5	33.0

Thus, if, as in 1 of Moore's cases, a male aged 42, the corrected calories per hour for the individual are found to be 68.39 and the body surface, 1.85 sq. meters,  $68.39 \div 1.85 = 36.97 =$  calories per sq. meter per hour. The normal according to the Aub-Du Bois table being 38.5,  $38.5 \div 36.97 = 1.041$ , that is, the metabolic rate for the individual is deficient to the extent of 4.1 per cent., and is expressed in round figures as — 4 per cent.

In certain newer methods, the body surface factor has been eliminated and the standards based on weight and age, with or without the stature. Among the most widely used formulas are those of Harris and Benedict, as follows:

For men and boys (down to 10 kilos.):

$$H = 66.473 + 13.752 w + 5.003 s - 6.755 a$$

For women (not under 21 years):

$$H = 655.096 + 9.563 w + 1.850 s - 4.676 a$$

(H = heat production in calories per 24 hours.

w = weight in kilograms.

s = stature in centimeters.

a = age in years.)

From these formulas the normal heat production for any given weight, height and age can be calculated and the results from tests in individual cases compared with the norm.

Dreyer has devised another formula, in which stature is disregarded and correlation based wholly on age and weight (as well as sex). The calculation is somewhat more intricate than in the methods above referred to, but was simplified by tables presented by Stoner (Boston Med. and Surg. Jour., Aug. 16, 1923, and Nov. 27, 1924).

The standards for children are still in a somewhat chaotic state. For females below 21 years of age, the standards of *Benedict and Talbot* (Carnegie Inst. of Wash., No. 302, 1921) and of *Benedict* (Boston Med. and Surg. Jour., Feb. 1, 1923) are recommended.

According to W. H. Stoner, *errors in metabolic rate determination* due to improper preparation of the subject are by far the greatest in magnitude as well as in frequency. Unless the subject has the customary light supper the night before and 12 to 14 hours of fast, of which at least 7 are spent in sleep; unless he has no breakfast; unless he is brought to the metabolism station without effort on his part, and given  $\frac{1}{2}$  hour of preliminary rest, and unless he is at ease physically and psychically, the result of the test cannot be considered basal. Among the sources of error in the technic are leaks in the apparatus, maladjustment of the nose-clamp and mouthpiece or mask, and infrequent renewal of the soda-lime.

P. Sainton and N. Péron maintain that in a given subject the most variable factor, with corresponding changes in the metabolic rate, is the respiratory output, *i.e.*, the amount of air breathed in and out in a given time. When once the metabolic rate has been determined in the usual way, subsequent changes in it can be followed with a fair degree of accuracy by simple determinations of the respiratory output with a mask and spirometer.

**CLINICAL FINDINGS AND APPLICATIONS.**—Deviations of 10 to 15 per cent. above or below the normal metabolic rate are not incompatible with a normal state of health. In a given individual, fluctuations of 2 to 5 per cent. may occur. As noted by E. F. Du Bois, the basal metabolism is increased in *hyperthyroidism*, in the *leukemias* (in direct proportion to the increase of white blood cells), in *nephritis*, *asthma*, *anemias*, *hypertension*, *acromegaly* and some *cardiac diseases*. In any of these it may run as high as + 40 per cent. In doubtful cases showing symptoms of both hypo- and hyperthyroidism, the metabolic rate is a most helpful adjunct; 15 per cent. above or below the average indicates a thyroid dysfunction unless there is another demonstrable cause. C. H. Frazier finds

the basal metabolism useful in deciding whether the operative procedure in hyperthyroid cases is to be a preliminary ligation or a primary subtotal thyroidectomy; in 70 per cent. of cases with the rate not above + 40 the gland is removed without the preliminary operation.

The determination of the basal metabolic rate should, as advised by Mohler, be made in every case of *goiter* with impaired health with the view of determining if the illness is dependent upon the goiter or is due to other causes.

To the group of cases of *disturbed thyroid activity* belong many cases of so-called *disordered action of the heart* seen in soldiers during the World War, *neurocirculatory asthenia*, *nervousness*, *weakness*, *loss in weight*, *incipient tuberculosis*, *syphilis*, and *gastrointestinal disturbances*. These conditions become more difficult to diagnose if a functional enlargement of the thyroid gland is present. Determination of the basal metabolic rate is of great help in ruling out thyroid etiology and therefore in directing proper treatment. Many of the *thyroid enlargements*, especially in young women, during menstruation or pregnancy, which are functional in character, cause considerable anxiety to the individual. Under these conditions a basal metabolism determination may be of great value in allaying unjustified fears. In *tumors of the thyroid*, the nature of the growth may be such as to destroy gland tissue and produce hypothyroidism, or, on the other hand, may stimulate the thyroid to increased activity. Some tumors, however, produce no variation in the basal metabolic rate. There are also individuals presenting all or some of the symptoms of hyper- or hypothyroidism, but in whom the thyroid gland is not palpable. Estimation of the basal metabolic rate under these conditions will reveal the actual activity of the gland. In this connection it should be borne in mind that enlargement of the thyroid gland may accompany *hypothyroidism*. In all suspected cases of deficient activity of the gland in which but few or only a single symptom of hypothyroidism is present, determination of the basal metabolic rate may throw light on the underlying condition. In *exophthalmic goiter* the procedure is of assistance in determining upon the kind of treatment, its

frequency, and its results, the justification and safety of surgical procedures, the severity of the intoxication, and the prognosis. In *polyglandular disturbances* it may be of great help, particularly in determining defect of glands other than the thyroid.

The following is a list of the range of *metabolic rates* found in various diseased conditions, as given by Mohler, the figures having been taken largely from the publications of E. F. Du Bois and his collaborators:

Per cent. basal metabolism above or below average normal.			
Normal .....	- 15	to	+ 15
Obesity .....	- 14	to	+ 10
Diabetes mellitus:			
Severe .....	- 19	to	+ 23
After fasting .....	- 36 (lowest observed)		
Emaciated .....	- 37	to	- 10
Cardiorenal without dyspnea .....	- 10	to	+ 10
Cardiorenal with dyspnea .....	- 25	to	+ 50
Nephritis with edema .....	- 40	to	+ 14
Nephritis without edema .....	- 2	to	+ 29
Pernicious anemia .....	- 2	to	+ 33
Leukemia .....	+ 21	to	+ 123
Typhoid fever .....	as high as		+ 50
Tuberculosis (temperature about 104° F.) .....			
.....	+ 15	to	+ 35
Tuberculosis (no fever) .....	- 33	to	+ 15
Prolonged undernutrition .....	- 30	to	- 10
Exophthalmic goiter:			
Very mild .....	+ 15	to	+ 30
Mild .....	+ 30	to	+ 50
Severe .....	+ 50	to	+ 75
Very severe .....	over		+ 75
Cretinism and myxedema .....	- 40	to	- 15

McCann warns that even if the metabolism is determined by the most accurate technique, under controlled conditions, a deviation from the normal can be properly interpreted only in the light of a thorough clinical study.

A. S. Jackson (Med. Jour. and Rec., May 7, 1924) found the basal metabolic rate of great value in the differentiation of mild, incipient cases of *exophthalmic goiter* from those of *cardiac neurosis*, *chronic nervous exhaustion*, *neurasthenia*, and the nervous phenomena of the *menopause*. In girls a symmetrical thyroid enlargement at *puberty* may be accompanied by nervous symptoms, tachycardia and palpitation, and in a few of these, thrills and bruits are present; a normal metabolic rate will assure the clinician that he is dealing with a vascular colloid goiter. In *hyperthyroidism* the metabolic rate is *not* an index of the patient's ability to withstand operation. A case with a rate of +44, but of only 3 months' standing, with recent rapid loss of weight and strength, beginning gastrointestinal disturbances and on the verge of a crisis, was considered a far poorer operative risk than one with a rate of +92 that

had passed through a crisis and had a period of comparative remission of symptoms. In the latter case ligation was performed with only a mild reaction. Pre-operative administration of Lugol's solution reduced the metabolic rate an average of 20 points in 30 cases, with proportionate clinical improvement. In *colloid goiter* the metabolic rate is chiefly of value in following the course of medical treatment with iodine, thyroid extract or thyroxin and determining the tolerance for them. Certain patients tolerate thyroid extract better than iodine and show much greater improvement with one than with the other. By pushing medication in children with colloid enlargement and yet keeping the rate between +5 and +15, one can greatly reduce or completely dispel many of the enlargements. In *hyperthyroidism* the diagnosis is frequently overlooked and treatment for chronic nephritis or anemia continued for long periods without result. A metabolic rate of -15 or more at once settles the matter. A variable rate is the rule in diseases of the other endocrin glands and in diseases such as *pernicious anemia*, *pellagra*, *epilepsy*, *diabetes*, *arthritis* and *Hodgkin's disease*. Tables bearing on 470 cases are presented by Jackson:—

TABLE I.  
STUDY OF THE BASAL METABOLIC RATE IN  
470 PATIENTS.

	Number of Patients	Average Basal Metabolic Rate
Exophthalmic goiter.....	56	+54
Adenoma with hyperthyroidism.....	60	+38
Adenoma without hyperthyroidism .....	78	+6
Colloid goiter.....	47	+2
Malignant thyroid.....	3	+12
Myxedema.....	2	-24
Hypothyroidism.....	15	-15
Obesity.....	12	-2
Neurasthenia.....	12	+8
Chronic nervous exhaustion.....	24	+7
Normal.....	31	+5
Cardiac neurosis.....	30	+10
Hypopituitarism.....	10	-11
Pellagra.....	1	+9
Addison's disease.....	2	-6
Pernicious anemia.....	7	+2
Diabetes.....	12	-6
Pregnancy.....	8	+8
Miscellaneous.....	60	+5

TABLE II.  
THE BASAL METABOLIC RATE IN EXOPHTHALMIC  
GOITER.

Average preoperative rate.....	+54
Maximum rate.....	+92
Minimum rate.....	+25
Rate after one ligation.....	+39
Rate after two ligations.....	+33
Rate after thyroidectomy.....	+6



In 3 diseases commonly confused in their early stages—*hyperthyroidism*, *neurocirculatory-asthenia* and *pulmonary tuberculosis*—the metabolic rate is of great diagnostic aid, especially if thyroid enlargement co-exists, according to Mohler. In *obesity*, it distinguishes the cases due to diminished thyroid and pituitary activity, these always showing a subnormal rate. It is of prime importance in obese subjects with organic heart disease, especially if hypothyroidism is suspected, as alarming symptoms may be produced by thyroid extract in the obese with heart disease if the cause of the obesity is overeating and physical inactivity. In the nervous manifestations at the *menopause*, the metabolic rate will help decide for or against thyroid therapy. In many disease conditions there are phenomena which of themselves will increase the metabolic rate, *e.g.*, chills, sweats, fever, dyspnea, exercise, food emotion, apprehension, anger, fright, tremor and menstruation.

G. Marañón and E. Carrasco (Ann. de méd., Feb., 1923) refer to a case of *acute hyperthyroidism* so intense as to render walking, use of the upper limbs and speech difficult, in which the metabolic rate was +150. The highest rate found in the literature was one of +170 recorded by Elliot. The writers agree with others who have pointed out a relationship of the degree of hypermetabolism to that of the tachycardia. Between the weight and metabolic rate there is not always a direct relationship, since a case may show marked variations in rate without any notable change of weight. Some cases of *Graves's disease* remain well nourished in spite of the typical symptoms and rise of metabolic rate. In the *pseudo-hyperthyroid vegetative neurosis* (comprising neurasthenia, circulatory neurosis, irritable heart, vagotonia, etc.), the metabolic rate is far more helpful diagnostically than the adrenalin or thyroid test and the differential leukocyte count, though even so, doubt is not always removed, since in most instances the figures obtained are not over 20 points away from the normal. *Ovarian insufficiency*, which lowers the metabolic rate, often accompanies hyperthyroid states, and when it is pronounced, may even reduce the rate below normal, as not infrequently happens in menopause cases with slight hyper-

thyroidism. As some hyperthyroid cases show, superadded to their steady tachycardia, paroxysmal tachycardial attacks, the metabolic rate is useful in determining whether *paroxysmal tachycardia* in any given case is based on hyperthyroidism. In 1 case paroxysmal tachycardia was coupled with transient edema and a rapid gain in weight; the metabolic rate being —16, thyroid gland was given, resulting not only in reduction of weight but also notable improvement of the tachycardia.

Any low metabolic figure suggests a thyroid inadequacy and justifies thyroid therapy, even if the clinical evidences of *hypothyroidism* are doubtful. *Exophthalmos* not of thyroid origin is differentiated by the metabolic rate. A young woman with menstrual disturbances, transient edema, rather pronounced *vegetative symptoms* and slight thyroid enlargement had been treated without success for hyperthyroidism; the metabolic rate proving to be —18, iodine and thyroid extract were given, which increased the nervousness and insomnia but removed the edema and improved the metabolic rate; after an intermission, thyroid extract was resumed, whereupon the nervous symptoms also finally disappeared and the case was cured in 1 month. In 7 cases of hyperthyroidism attending the *menopause* the writers found metabolic rates ranging from +20 to +90; in 5 of these cases a goiter had become toxic at this period. In a case of *post-operative menopause* the rate was —11, and marked improvement followed thyroid and ovarian treatment. Two cases of *adiposogenital syndrome* showed rates of 0 and —2, and 2 of *prepuberty pseudohermaphroditism* ("pre-adolescent type of hypopituitarism") showed —19 and —20. In *acromegaly* the metabolic rate is of much less value for diagnosis than as a guide for thyroid medication.

According to D. A. Haller and M. M. Clayton (Jour. of Lab. and Clin. Med., Apr., 1924) satisfactory basal metabolic tests in the physician's office are feasible with the Benedict portable apparatus. Among 291 patients the rate was above +10 in 110 (24 per cent.) and below —10 in 49 (11 per cent.). Among the latter 49, there was definite evidence of glandular system disturbance in 39 and probable evidence in 4. Of the remaining 6, 4 were

poorly nourished, 2 probably having *tuberculosis* and 2 *dementia precox*. A rate below —10 is usually of some diagnostic value. A normal rate clinimates hyperthyroidism as a diagnosis, but is not proof of thyroid adequacy.

The basal metabolic rate in *typhoid fever* has shown that toxic destruction of protein occurs in this disease and securely vindicated the high caloric diet. In *myelogenous leukemia* the increased rate parallels the number of immature myelocytes and leukocytes rather than the total white count, and may forecast an exacerbation some days before an increase in leukocytes occurs. No adequate explanation can be given for the increased rate in *pernicious anemia*. In *paralysis agitans* the increased rate is due to the inability of the patient to remain quiet (Fleming).

In regard to the *nephroses*, Bullowa notes that Epstein and Lande have shown the association of diminished basal metabolism, edema and a high cholesterinemia. Thyroid extract is of value in obstinate edemas in this condition, and the high nitrogen diet may act in them by stimulating the thyroid. Metabolic rate determinations segregate the edemas amenable to thyroid therapy.

Wakeham showed that there is a premenstrual rise of metabolic rate, and thereafter a distinct fall during or immediately after *menstruation*. H. F. and H. K. Root found a marked increase during the later months of *pregnancy*. Kraul and Halter observed a reduction of rate by 17 to 30 per cent. in 4 women after *ovarian sterilization* with the X-ray. In *uterine fibroid* cases the average rate was +30; this increased rate was lowered by hysterectomy.

In *premature infants*, Talbot and his co-workers found heat production very low when calculated on the basis of total production per 24 hours or per unit of body surface. The basal metabolism remains lower than that of the full-term infant for at least 3 months. Hence the need of great protection against heat-loss for the premature baby.

In *psychoneurotic patients* without goiter Ziegler and Levine (Amer. Jour. Med. Sci., Jan., 1925) found the metabolic rate increased when these patients thought about an emotion-producing aspect of their past history. The commonest objective re-

sponses to emotion-producing stimuli were slight changes in the color of the skin, slight changes in the rate and amplitude of respiration, and very fine tremors.

As regards the possible effects of *drugs* on the metabolic rate, W. M. Boothby and L. G. Rowntree have made a study of 25 drugs, such as acetylsalicylic acid, barbital, caffeine, cinchophen, codeine, iodides, morphine, radium water, strychnine and sulphomethane. Given in single, moderate doses these did not influence the metabolic rate. Only *adrenalin* (0.5 Gm.) produced consistent changes of more than 10 per cent. in the rate within 2 hours of administration; a definite elevation of the respiratory quotient took place within this period. *Caffeine* seems to increase heat production, but only in large doses. *Morphine* in sufficient quantity to produce sleep lowers heat production. *Insulin* does not seem to possess a direct calorogenic action, but increases the rate in the fasting subject if the blood sugar falls to a critical level associated with symptoms of hypoglycemia. *Thyroxin*, like adrenalin, has a definite calorogenic action, but one which does not appear for several hours and reaches its height after several days. In metabolic rate tests neither adrenalin nor insulin should be given within several hours preceding the test. No test made within several weeks after taking thyroxin can be assumed to represent the lowest metabolism of the individual. *Iodides* do not affect the metabolism of a normal subject, but may convert a case of adenomatous goiter without hyperthyroidism into one with hyperthyroidism and correspondingly increased metabolism. S.

**BELLADONNA.**—Belladonna is a solanaceous plant, the *Atropa belladonna*, or deadly nightshade, which is indigenous to southern Europe and central Asia. The leaves and root are used in medicine, and also its important alkaloids, *atropine*, which occurs in the plant in combination with malic acid as a bimalate, and *hyoscyamine*, very similar to atropine.

#### PREPARATIONS AND DOSES.

—The official preparations are:—

Belladonna leaves, or *Belladonna folia*, which have a slightly bitter and disagreeable taste, and contain at least 0.3 per cent. of alkaloids. Dose, 1 to 3 grains (0.065 to 0.2 Gm.).

The leaves are used to prepare:—

The extract of belladonna, or *Extractum belladonnae* (1.25 per cent. alkaloids). Dose,  $\frac{1}{10}$  to  $\frac{1}{2}$  grain (0.0064 to 0.03 Gm.).

The fluidextract of belladonna leaves, or *Fluidextractum belladonnae foliorum*. Dose, 1 to 3 minims (0.065 to 0.2 c.c.).

The tincture of belladonna, or *Tinctura belladonnae* (0.03 per cent. alkaloids). Dose, 5 to 20 minims (0.3 to 1.25 c.c.).

The belladonna plaster, or *Emplastrum belladonnae*, containing extract of belladonna corresponding to not less than 0.25 per cent. of the alkaloids.

The belladonna ointment, or *Unguentum belladonnae*, which contains 10 parts of extract of belladonna, 5 of dilute alcohol, 30 of wool fat, 5 of yellow wax, and 50 of petrolatum.

The root, *Belladonna radix*, contains at least 0.45 per cent. of alkaloids. Dose,  $\frac{3}{4}$  to 2 grains (0.05 to 0.13 Gm.). It is used to prepare:—

The fluidextract of belladonna root, or *Fluidextractum belladonnae radices*. Dose,  $\frac{3}{4}$  to 2 minims (0.05 to 0.13 c.c.).

The belladonna liniment, or *Lini-mentum belladonnae*, N. F., composed of fluidextract of belladonna root, 950 parts, and camphor, 50 parts.

Of the active principles the following preparations are official:—

Atropine, or *Atropina*, occurs in the form of white, amorphous, acicular crystals or powder having an acid, bitter taste. One Gm. is soluble in 455 c.c. of water, 2 of alcohol, 25 of ether, 1 of chloroform, and 27 of glycerin.

Dose,  $\frac{1}{120}$  to  $\frac{1}{60}$  grain (0.0005 to 0.001 Gm.).

Atropine sulphate, or *Atropinae sulphas*, which occurs as a white powder having an intensely bitter and disagreeable taste. One Gm. is soluble in 0.4 c.c. of water, 5 of alcohol, 420 of chloroform, and 3000 of ether. Dose,  $\frac{1}{150}$  to  $\frac{1}{60}$  grain (0.0004 to 0.001 Gm.).

(For *hyoscyamine*, see *HYOSCYAMUS*.)

**INCOMPATIBLES.**—Atropine is chemically incompatible with the alkalies, tannin, and the salts of mercury; it is physiologically incompatible with morphine (opium), pilocarpine, muscarine, aconitine, and eserine (physostigmine).

The action of belladonna and its alkaloids is antagonized by muscarine and partly so by pilocarpine, physostigmine, and aconite. Opium and its analgesic derivatives oppose its action on the cerebrum, pupil, and respiration.

**PHYSIOLOGICAL ACTION.**—The physiological action of belladonna is essentially that of atropine.

Atropine frequently exerts a quieting action in very nervous infants, and sometimes checks habitual vomiting and pylorospasm. In studies on 100 infants the writer found it to act most promptly and with smallest doses when given before meals. The only reliable mode of administration proved to be in a 0.5 per cent. alcoholic solution. The initial dose should not exceed 0.0001 Gm. ( $\frac{1}{650}$  grain); this is the amount present in 1 drop of the solution. An infant of 8 months received ascending amounts up to 0.006 Gm. ( $\frac{1}{11}$  grain) a day without any untoward result. Lindberg (*Acta Pæd.*, July, 1925).

**Nervous System.**—Atropine has no conspicuous effect on the brain and spinal cord when administered in

therapeutic doses, but it depresses certain peripheral nerve-endings, especially those in the heart and secretory organs, such as the salivary and sudorific glands, thus reducing their secretions: the saliva and sweat in the examples given. The nerve-endings in certain involuntary muscles, such as the constrictor of the iris, the ciliary muscles, and the muscular coat of the bronchial tubes, are likewise depressed. In excessive doses it excites the brain, producing delirium, with hallucinations, incoherent speech, laughter, and motor restlessness, these effects being followed, after a time, by quietude and stupor. The medulla and cord are also stimulated and then depressed by atropine, but these effects are less marked than those on the brain.

The effects on the nervous system are often overlooked. It happens occasionally that because of the attendant delirium a subject is rushed to an asylum. In any suspected case any suspicious beverage or medicine in evidence can be used to test, a drop of this being instilled into a cat's eye. This failing, a drop of the patient's urine may serve the same purpose. Hunziker (*Correspond. Blatt f. schweizer Aerzte; Druggist Circular*, Dec., 1916).

**Circulation.**—In moderate doses atropine depresses the vagal nerve-endings of the heart, while strongly stimulating the vasomotor center and also, but to a slight degree, the heart-muscle. As a result there occur increase of the pulse rate and a rise of the blood-pressure. Toxic doses cause a secondary depression of the circulation. Another effect observed under the influence of therapeutic, and very often of toxic, doses is a scarlet flushing of the skin affecting first the face and neck and then the

chest. This is due to dilatation of the cutaneous vessels, and is believed to be of central origin, since cutting of the sympathetic prevents this phenomenon. This superficial dilatation is not sufficient, however, to counteract the rise of blood-pressure caused by the constriction of the internal vessels. Nor is it accompanied by sweating, since the sweat-glands are paralyzed early in the course of the process.

The writer reached, after an experimental study, the general conclusion that at the outset atropine causes augmentation of the excitability of the cardio-inhibitory elements of the vagus. This increased excitability is not merely apparent but is genuine. Petzetakis (*Presse méd.*, Dec. 4, 1916).

**Respiration.**—Full therapeutic doses stimulate the respiratory center, causing rapid and deep breathing. Under the influence of poisonous doses, the center becomes secondarily depressed, causing death from asphyxia.

Any respiratory stimulation due to atropine is to be explained by (1) the increased "dead space" or dilatation of the bronchi, and (2) increased metabolism. The metabolism being increased, the respiratory volume increases to rid the body of CO<sub>2</sub> produced, and for a unit of CO<sub>2</sub> eliminated, the respiratory volume increases because of an increased "dead space." Higgins and Means (*Jour. of Pharm. and Exper. Therap.*, July, 1915).

**Eye.**—Taken internally in full doses or locally applied, atropine causes marked dilatation of the pupil, with loss of the light reflex and a tendency to increased intraocular tension. Paralysis of accommodation is also produced. These effects are due to depression of the oculomotor

endings in the circular muscle of the iris and ciliary muscle.

**Secretions.**—Atropine reduces or actually checks the activity of all structures, excepting the kidneys. The saliva, gastric juice, sweat and mucous secretions of the respiratory tract are the most strongly affected; the pancreatic juice and bile, to a less extent. The drug finally paralyzing the endings of secretory nerves, it causes dryness of the mouth, thirst, anorexia, dryness of the skin, elevation of the superficial temperature, and hoarseness. In nursing women the mammary secretion is reduced, though not entirely checked, by atropine.

**Involuntary Muscles.**—In very small doses atropine increases slightly intestinal peristalsis, probably by depressing the inhibitory (splanchnic) nerve-endings in the intestinal walls in the same way that it depresses the vagal endings in the cardiac muscles. Full doses, on the other hand, exert a depressant, or at least a controlling, effect on involuntary-muscle tissues in general. In the case of the intraocular muscles, the muscular coat in the bronchial tubes and esophagus, this effect is due to paralysis of the terminals of the motor nerves distributed to these muscles. In the case of the stomach, intestine, bile-ducts, ureters, uterus, and bladder, however, the nervous control of the involuntary muscle-tissue is not affected. Small doses of the drug tend, under normal conditions, rather to stimulate muscular activity in these organs than to depress it, but, when abnormal stimuli to contraction of the muscle occur which tend to produce spasm, these small doses depress the muscles and thus tend to prevent

spasm. In toxic doses or when applied locally atropine paralyzes involuntary muscular tissue directly.

**Temperature.**—Atropine causes a rise of temperature by arresting the action of sweat-glands and thus reducing heat dissipation.

**Local Action.**—Atropine is practically non-irritating. Used locally in sufficient concentration, it depresses sensory and motor nerve-endings, involuntary-muscle tissue, and also glandular tissues.

[From my viewpoint all the above phenomena which appear confusing, though representing the prevailing classic interpretation of the action of atropine, may be explained without difficulty in the following way: Atropine excites more or less actively the sympathetic center, which in turn governs the *propulsive* activity of the arterioles and, therefore, the volume of blood these minute arteries admit into the capillaries of all tissues. A therapeutic dose of atropine enhances, therefore, the functional activity of a tissue by causing more arterial blood to enter that tissue; it will increase peristalsis for example by admitting an excess of blood into the muscular coat of the intestine. But toxic doses have a different effect: they so excite the arterioles that they cause excessive constriction of the vessels, thus reducing their caliber to such an extent that the blood admitted to the tissues is inadequate to enable them to carry on their function. A toxic dose will thus arrest or inhibit peristalsis by reducing or even arresting the arterial blood admitted to the intestinal muscular coat and likewise the secretory activity of glands by inhibiting the activity of their secreting cells, etc. For further details on this interpretation the reader is referred to my work on the "Internal Secretions," 5th ed., p. 1210. C. E. DE M. S.]

The volume of the normal saliva, its amylolytic power, and the amount and percentage composition of solids secreted remain approximately constant during a continuous period of secretion of 6 or 8 fifteen-minute

periods. If there is any change, it is a very slight falling off of the percentage composition of organic solids and at times of the amylolytic power. Atropine diminishes the amylolytic power of the saliva from 15 to 30 per cent. Both the amount and percentage composition of total solids secreted are greatly diminished by atropine. The decrease is in the organic constituents. E. M. Ewing (*Jour. of Pharmacol. and Exper. Therap.*, Sept., 1911).

**Clinical Effects.**—These have been so carefully studied by John Harley that his version is presented here with but few changes:—

If the minimum therapeutic dose,  $\frac{1}{120}$  grain (0.0005 Gm.), be injected beneath the skin of a healthy adult, there will be noticed, after ten to twenty minutes, a quickening of the pulse, and generally a small increase in volume and power. This change will be very decided if the pulse was previously slow and feeble. The increase in the number of pulse-beats will generally amount to 20 per minute; it will take place suddenly, and attain its maximum within one or two minutes. In about half an hour a gradual decline takes place and the heart soon returns to its usual state, and continues to beat as quickly and powerfully as before. Just as the pulse rises, a slight giddiness is often perceptible. Usually these will be the whole of the symptoms; but in weak and delicate adults, a feeling of dryness of the mouth and throat, and, at the end of an hour or two, a slight dilatation of the pupil, in a subdued light, will be superadded.

When  $\frac{1}{60}$  grain (0.001 Gm.) is used, the acceleration of the pulse will be found to range between 20 and 60

beats, the rise being attended by considerable giddiness and waviness of the vision. The patient walks cautiously, and with an inclination to unsteadiness. After twenty to forty minutes he will complain, with some huskiness of voice, of great dryness of the throat and mouth, and the anterior part of the tongue or the whole of the dorsum, excepting a wide margin, will be found dry, brown, and rough. The hard palate, and in many persons the soft palate also, will be perfectly dry and glazed. There will be more or less somnolency, and sometimes a little flushing of the face. The dilatation of the pupils will amount to  $\frac{1}{4}$  or  $\frac{1}{6}$  inch.

The effects of  $\frac{1}{48}$  grain (0.00135 Gm.; a slightly toxic dose) are as follows: After ten or fifteen minutes an acceleration of the pulse of from 20 to 70 beats; no apparent change in volume, but a decided increase in the force of the cardiac contractions and of the arterial tonus; a general diffusion of warmth, a slight throbbing or heaving sensation in the carotids, and a feeling of pressure under the parietal bones; giddiness, heaviness, drowsiness, or actual sleep, with great tendency to dreamy delirium, and, in women, slight occasional startings; complete dryness of the tongue, roof of the mouth, and soft palate, extending more or less down the pharynx and larynx, rendering the voice husky, and often inducing dry cough and difficulty in swallowing; parched lips, occasional dryness of the mucous membranes of the nose and eyes, and increasing dilatation of the pupils. After about two hours the dryness of the mouth is relieved by the appearance of a viscid, acid

secretion of an offensive odor, like the sweat of the feet; the mouth becomes foul and clammy, and a bitter, coppery taste is complained of; but as moisture returns to the mouth, the pulse is observed to fall, and it now rapidly regains its ordinary rate and character. The pupils have now reached their maximum dilatation and measure about  $\frac{1}{5}$  inch; but when exposed to bright light, they will still contract to  $\frac{1}{6}$  or even  $\frac{1}{8}$  inch, according to their original size. Slight elevation of surface temperature is noticed during the action of the medicine, rarely exceeding  $1^{\circ}$ , and a still less elevation of the internal temperature of the body. No difference will be observed in the rate of the respiration, except (in nervous women) a little emotional excitement on the sudden accession of the giddiness. The breathing will be tranquil, the patient occasionally heaving a deep sigh, and still oftener taking a prolonged yawn, as he sits still in a dull, apathetic or drowsy condition. After the pulse has resumed its ordinary rate, and the mouth has become moist, the giddiness and drowsiness pass off, and the patient appears tolerably lively and brisk in mind and body. But he will himself continue to feel for some hours longer such languor of body and mind as will render him disinclined for, or even incapable of, active bodily or mental exertion. Slight dimness of vision also remains, and the patient is unable to thread a needle, or even to read.

If larger doses be given, there will be superadded a distressing fluttering sensation in the cardiac region, slight delirium; exquisite sensibility of

hearing, and frequent illusions of this sense also; staggering, or complete inability to walk; insomnia, restlessness, and frequently great nervous agitation of mind and body. Nausea and headache are rare and exceptional consequences of the subcutaneous use of atropine, but sometimes follow when it is given by the stomach in full doses.

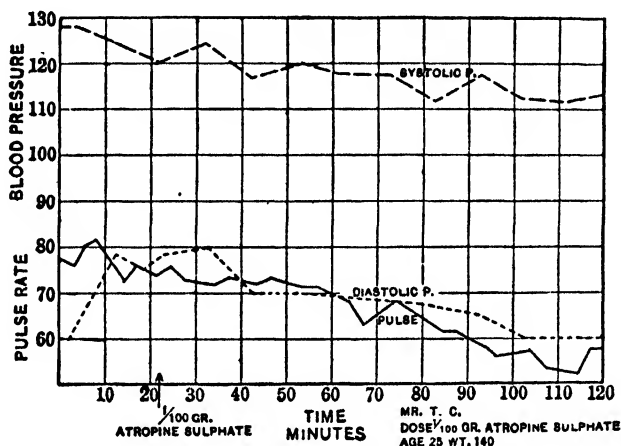
Certain conditions modify the action of atropine. Children are more tolerant of the drug than adults, and in this respect resemble the lower animals; and while acceleration of the pulse, dilatation of the pupils, and dryness of the mouth are more readily induced in them, cerebrospinal effects—giddiness, drowsiness, sensory illusions, and unsteadiness of gait—are only developed after a very large dose. Pregnancy appears to diminish the activity of atropine. The weak, and those of excitable temperament, are more readily and powerfully influenced than the strong. In renal disease, when the secretion of urine is diminished, or only moderate in quantity, the effects of atropine are readily induced and considerably prolonged; in persons with unusually active kidneys the action of the drug is less pronounced. While atropine in contact with caustic soda and potash is decomposed in the course of two or three hours, these bodies have no power of annulling or even diminishing the action of the alkaloid within the body. Acids have no particular influence on the action of atropine. When administered by the stomach, the action of the drug is sometimes delayed for two hours, and then develops suddenly.

Atropine passes undiminished and

unchanged through the blood. The presence of atropine in the urine may be shown by dropping one or two drops of the urine within the eyelids of another person or animal at intervals of ten to twenty minutes for two or three hours and noticing its dilating action on the pupils. The atropine may be separated from the urine by shaking the latter with a quantity of chloroform equal to a sixth of its bulk and separating the chloroform or allowing it to evaporate spontane-

in which there was little or no slowing or even a slight hastening, further reduction of dosage nearly always resulted in a slowed heart, these subjects being evidently more susceptible to the drug than the others. A larger dose— $\frac{1}{50}$  grain (0.0013 Gm.)—caused a preliminary brief slowing followed by a considerable rise (up to 100 per minute) lasting 4 hours, succeeded, in turn, by a slowing (to about 60) which continued the rest of the day.

The skin becomes the seat of a sensation of warmth followed by a temporary blush, and in children and



Slowing of pulse-rate and lowering of blood-pressure after  $\frac{1}{100}$  grain of atropine sulphate. (Rudolf and Bulmer, in *Amer. Jour. Med. Sci.*)

ously. The remaining stain is dissolved in a few drops of water, and a drop placed within the eyelids. The  $\frac{1}{96}$  grain (0.00067 Gm.) of atropine sulphate (sufficient to kill an infant) may thus be detected.

Rudolf and Bulmer (*Amer. Jour. Med. Sci.*, Nov., 1924), in numerous clinical tests with small doses of atropine, found that single doses of  $\frac{1}{100}$  grain (0.00065 Gm.) given hypodermically or by mouth nearly always cause a distinct *reduction in the pulse-rate*, continuing for many hours—often all day after a dose given at 8 A.M. In 3-day tests in which a single such dose was given only on the 2d day in some 50 individuals, the average pulse-rates for the 3 days were 80.22, 75.5 and 80.45. In the few instances

adults of light complexion is sometimes followed by a scarlet suffusion. In persons subject to vascular irritation of the skin the redness is persistent, and may be followed by slight roughness and desquamation.

After large doses insomnia and delirium arise and poisonous doses prolong these effects for hours. Thereafter coma gradually supervenes. Headache, vertigo, illusions, hallucinations, a busy delirium, and sometimes somnolence occur. Giddiness and muscular weakness, with incapacity for exertion, accompany the hypnotic effect, while restlessness and insomnia occur



when the hypnosis is overruled by the excitant action. The spinal cord is least of all affected by atropine.

**ATROPINE POISONING.**—This may be produced either by the ingested alkaloid itself or by any of the crude drugs containing it, especially belladonna. It can also occur, and frequently does, owing to the large doses dropped into the eyes by ophthalmologists, by absorption from the eye, and also from the skin when, for instance, an excessive quantity of the belladonna ointment is used.

The writer has often observed evanescent erythema of the face, chest, and abdomen follow instillations of 0.5 to 1 per cent. aqueous solution of atropine in children aged between 2 and 7 years. Prostration or delirium, so frequently noted in adults, was never observed. In some children the erythema regularly followed each instillation. Most of the subjects were affected with phlyctenular ophthalmia, arguing a reduced condition of the system. The phenomena were particularly noted during the inflammatory attacks, much less frequently in intervals of quiescence. These accidents became very infrequent when collyria in oil were substituted for the aqueous; if the latter are employed the lachrymal puncta should be compressed with the finger. *Colin (La Clin. Ophthalmol., Dec. 10, 1910).*

The likelihood of toxic phenomena is greater when the alkaloid is administered hypodermically than when given by the mouth.

The early signs of atropine poisoning, those which denote the so-called "physiological limit," are: dryness of the mouth and throat, with redness and occasionally pain; dilatation of the pupils, with imperfect vision; a rapid, high-tension pulse, and hot, dry skin. These signs indicate that

the drug should not be pushed further. When this limit is exceeded, there appears an erythematous rash resembling that of scarlet fever on the face, neck, and body, often accompanied by dysphagia, a sensation of burning in the throat, and hoarseness, the patient becoming by that time very restless. Acceleration of the respiration, extreme rapidity of the pulse, and muscular inco-ordination, with more or less increase of the reflexes, then develop. A prominent symptom at about this time is delirium, generally with noisy, disconnected talk and hallucinations, occasionally with violent motor excitement, and even convulsions, leading finally to stupor.

[This typifies, in the light of my interpretation of the action of atropine, the period during which it increases violently the propulsive activity of the arterioles, thus driving an excessive quantity of arterial blood into the cellular elements of all organs and causing violent hyperemia of the skin (erythema), brain (delirium), spinal cord, and peripheral sensory elements (convulsions), etc. C. E. DE M. S.]

More or less generalized eruptions not only occur from the internal administration of belladonna or its alkaloid, atropine, but also from absorption through the skin of local applications of the same. The skin does not have to be broken or denuded of epidermis for absorption to take place; the symptoms of poisoning, however, develop much sooner if such is the case. The great majority of the cases exhibit an erythematous or scarlatinal type of eruption, which is more frequently found on the face and the upper portion of the body, but in a fair number of cases the outbreak is generalized. Gangrenous, purpuric, and eczematous eruptions have been reported. Although in a great many instances severe symptoms of poisoning are

present, the eruption may be unaccompanied by other manifestations of drug absorption. The prognosis is favorable. Belladonna may also produce an eruption from a local irritant effect. F. C. Knowles (Amer. Jour. Med. Sci., July, 1911).

Three cases of belladonna poisoning in little children, aged respectively 4, 5 and 6 years, due to eating of the purple berries picked by them from fruiting *Atropa belladonna* shrubs in a public garden. All 3 recovered under appropriate treatment, **gastric lavage** having brought away the berries. Mary E. Joll (Lancet, Oct. 7, 1916).

A woman with gall-stones used a suppository containing 0.015 Gm. ( $\frac{1}{4}$  grain) of atropine, the druggist having evidently confused the latter with belladonna extract. Severe symptoms followed, including delirium, auditory hallucinations and stupor, but no rash nor disturbances of speech or swallowing. **Pilocarpine** and **coffee** were mainly used. All the symptoms passed off in 4 days. Malade (Münch. med. Woch., Jan. 19, 1923).

In spite of these alarming symptoms, which may end in death in from five to twenty hours, a fatal ending occurs only in a small number of cases (about 12 per cent.). In the fatal cases the primary respiratory stimulation is followed by depression of the respiratory center; the circulation also fails, and death occurs from asphyxia.

Several cases have been reported in which poisoning followed the application of belladonna plasters.

Case of poisoning from belladonna plaster in a healthy man. The plaster, 6 by  $4\frac{1}{2}$  inches, had been applied to his back for the relief of pain at about 11 A.M., and by 2 P.M. the patient had become delirious, maniacal, and irresponsible. He had dryness and redness of the skin, the pupils were dilated, the pulse 130, and respiration 40 per minute. The plaster was removed and his condition

improved by evening. Two days later the only sign of belladonna poisoning which remained was some dilatation of the pupils. He had no memory of what had occurred. B. G. R. Crawford (Brit. Med. Jour., Aug. 11, 1917).

Case of poisoning in a woman from prolonged application to the back of a liniment containing 4 drams of belladonna tincture. She did not respond to morphine, but 6 drops of **Lugol's solution** hourly and  $\frac{1}{4}$  grain (0.015 Gm.) of **pilocarpine hydrochloride** proved helpful. H. Fried (N. Y. Med. Jour., Feb. 21, 1923).

**TREATMENT OF ATROPINE POISONING.**—The best antidote is **Lugol's solution** (the liquor iodi compositus). **Tannic acid**, 30 grains (2 Gm.) in water, or vegetable astringents containing it, including **tea**, are also valuable. The first step is to empty the stomach with the **stomach-tube**, or by means of an emetic, such as **apomorphine** ( $\frac{1}{10}$  grain—0.006 Gm.) hypodermically if the case is in the first stage. When the asthenic stage is reached, however, **zinc sulphate** ( $\frac{1}{2}$  dram—2 Gm.) by the mouth or **mustard** (2 drams—8 Gm.) in lukewarm water is safer. Any of the physiological antagonists of atropine, such as **pilocarpine** or **physostigmine**, may be cautiously given, but only in the early stages. **Morphine** is often recommended as an antidote, but the dose usually given,  $\frac{1}{4}$  grain (0.016 Gm.), should not be repeated, since it is not, as generally taught, a true antagonist of belladonna, serving chiefly to prevent or quiet the delirium, which is also relieved by an **ice-bag over the head**.

Morphine does not save life even in mild cases of belladonna or atropine poisoning. When the dose of the latter is sufficient to initiate the paralyzing phenomena in the nervous

system morphine is a dangerous agent. It is especially contraindicated when the case is comatose. Morphine on the whole should not be regarded as antagonistic of atropine. Roch (*Revue médicale de la Suisse romande*, Feb. 20, 1908).

**Pilocarpine**,  $\frac{1}{4}$  grain (0.016 Gm.); or **physostigmine**,  $\frac{1}{30}$  grain (0.002 Gm.), may also be employed to counteract the secretory paralysis, cardiac acceleration, and pupillary dilatation caused by atropine—aside from the true toxic effects. During the period of excitement, **ether** or **chloroform** may be required.

Six cases of belladonna or hyoscyamine poisoning, all terminating in recovery. The poison should be removed by **emetics**, followed by **lavage** after an injection of **morphine**. Purgatives and enemas are also useful in case the poison was taken by the mouth. If injected, the place of injection should be cut into and the blood squeezed out. **Potassium permanganate** is said to be a chemical antidote to atropine. The lavage can be done with water tinted with the permanganate to a pale bluish pink; the permanganate can be given internally in spoonfuls of a 0.25 to 0.5 per cent. solution. Husemann recommends administration of **tannin**, and others **iodine** and **potassium iodide**. Morphine is extremely valuable, but it has no action on the heart, and in case of stupor, coma, or paralysis it may do actual harm. In such cases **black coffee**, **camphor**, **caffeine**, **stimulation of the skin**, etc., are indicated. The nervousness and insomnia are best combated by **tepid baths**, and the patient should **drink** as copiously as possible. A large proportion of the atropine poisonings on record were due to carelessness in prescribing. Löbl (*Wiener klin. Woch.*, Bd. xviii, Nu. 34, 1905).

Case of poisoning in a child of 2 years in which there was a scarlet eruption very closely resembling that of scarlet fever. The tempera-

ture was normal; pulse, 180; pupils dilated and did not contract to light. The skin was dry; also the lips and tongue. It was quite clear that the child had taken an aqueous solution of atropine. She was quite nervous and fretful and seemed, by the twitching of the arms and legs, to be on the verge of a convulsion.

Treatment consisted of giving **paregoric**,  $\frac{1}{2}$  dram (2 Gm.), which soon quieted the child. It did not seem advisable to give an emetic, as the child had taken the poison some two hours previously. A solution of paregoric was left containing 15 minims (1 c.c.) to the dose to be given every two hours if the child became very restless. Two hours later the writer was called again, and remained all night at the bedside, and despite the administration of 15 drops (1 c.c.) of paregoric every hour the child did not sleep till near morning. Then he started with 2-grain (0.13 Gm.) doses of **tannic acid** every two hours. The child soon fell into a quiet sleep, and in twenty-four hours from taking the drug was in a normal condition. C. A. White (*Med. World*, Oct., 1911).

In a study of the action of the blood on atropine, the writers found that the substance in rabbit serum which annuls the toxic action of atropine is of the nature of a ferment. The reaction was positive in 30 per cent. of 10 patients with exophthalmic goiter and in 15 per cent. of 20 with ordinary goiter; it was never found in the 20 persons with apparently normal thyroids. Döblin and Fleischmann (*Zeit. f. klin. Med.*, lxxvii, Nu. 3-4, 1913).

During the second stage, that of circulatory and respiratory depression, **external heat**, stimulants, such as **caffeine sodiobenzoate**, **strychnine**, **digitalin**, etc., are indicated. **Artificial respiration** and **hypodermoclysis** of **saline solution**, or better **intravenous infusion** of the latter, are of great assistance, especially when we take into account the tendency to recovery

if life can be prolonged long enough by artificial means.

Retention of the urine being the rule in these cases, owing to paralysis of the bladder, the urine should be drawn with the catheter when six or eight hours have elapsed without urination.

**THERAPEUTICS.** — **External Uses.**—Belladonna liniment, plaster, and ointment are often employed to relieve pain, as local applications to painful areas. As the drug has to be used rather freely to get good results, some care is necessary to avoid general intoxication from absorption, especially in fair women and in children, owing to the thinness of their skin, or if the application is made where the skin is broken.

The plaster is very useful when applied over the seat of pain in **rheumatism**, especially **lumbago**, **neuralgia**, or when **abdominal pain** or **cardialgia** is only moderately severe. The ointment is also helpful when applied over chronically **inflamed joints**, oncoming **boils**, or other localized **inflammatory foci**. In painful **hemorrhoids** the following ointment is very helpful:—

℞ *Cocaine hydrochloride* ..... gr. ij (0.13 Gm.).  
*Extract of belladonna leaves* ... ʒj (4 Gm.).  
*Extract of hamamelis* ..... ʒij (8 Gm.).  
*Petrolatum* ..... ʒj (31 Gm.).

Ointment to be applied locally.

In **anal fissure** the same ointment serves both to relieve pain and reduce spasm of the sphincter ani, a troublesome feature of these cases. The liniment or ointment of belladonna is very helpful when applied over **swollen lymphatic**, **parotid**, or other

**glands**. It relieves the pain in **sprains**. The application of a mild sinapism, to redden the skin slightly, will increase the efficiency of the belladonna. In **blepharospasm** the extract or ointment may be rubbed on to the eyelids externally.

When the mammary glands are swollen or tender, either early in lactation or later, when we wish to arrest **lactation** (on death or removal of infant or weaning), atropine [4 grains (0.26 Gm.) to 1 ounce (31 Gm.) of rose water] is a clean and efficient remedy to apply to the glands. The gland is first cleaned with soap and warm water, carefully dried, and the solution of atropine applied to the surface (avoiding the nipple and the areola) with a camel's hair brush and allowed to dry. The glands should then be drawn upward and inward (to take off weight and tension) and retained by means of a proper bandage. If preferred, the breast may be enveloped in lint wetted with the above solution. If the pupils dilate and the mouth becomes dry, the application should be removed.

In **ophthalmology** atropine is employed a great deal locally not only as a therapeutic agent, but as an important aid in diagnosis. A couple of drops of a 4 grain (0.26 Gm.) to the ounce (31 Gm.) solution of atropine dropped in the eye causes complete pupillary dilatation in about twenty minutes and complete loss of the power of accommodation in one and one-half hours. The effect on the pupil persists a number of days, while on the ciliary muscle it may even last two weeks. In many persons the atropine is absorbed sufficiently into the general system to

cause unpleasant dryness of the mouth, anorexia, *i.e.*, the full physiological effects of the drug. A much weaker solution will dilate the pupil than is required to paralyze the ciliary muscle.

Study of the effect of atropine on the infant eye. The writers instilled 1 drop of a 1:1000 solution, diluted, in the eyes of 36 infants, making a total of 300 instillations. The effect of the drug did not differ materially from that obtained in adults. Ehrenreich and Riesenfeld (*Zeit. f. Kinderheilk.*, Feb. 14, 1921).

Atropine, 1 drop of a 1 per cent. solution 3 times daily for 4 or 5 days prior to examination, is the best cycloplegic, although, except in a few instances, a 0.5 per cent. hyoscine solution is almost as satisfactory and has the advantage of producing a rapid cycloplegia, while its effect is sufficiently evanescent. Homatropine in 2 per cent. solution has the most evanescent effect, and though less certain in some instances, is satisfactory in a large proportion of cases. A. E. Bulson, Jr. (*Jour. Ind. State Med. Assoc.*, June, 1923).

The uses of atropine may be summarized as follows: 1. To dilate the pupil, in order to facilitate examination of the retina and lens (though for this purpose more rapidly acting mydriatics, such as homatropine, are preferable). 2. To paralyze accommodation, so that the refractive condition of the eye in its resting state can be ascertained and proper glasses prescribed. 3. In certain inflammatory diseases of the eye to give it rest by paralyzing its muscles, to relieve local pain, or prevent blocking up of the pupil with pus and adhesions of the iris to the lens.

Mild solutions [1 or 2 grains (0.065 or 0.13 Gm.) to 1 ounce (31 Gm.)] instilled within the eyelids generally give prompt relief in all superficial

inflammatory conditions of the eye in which pain, tenderness, and photophobia are present. In strumous **corneal ulcers** and **phlyctenular keratitis** (by diminishing photophobia and blepharospasm and lessening blood-supply) a few drops of a mild solution [1 grain (0.065 Gm.) to 1 ounce (31 Gm.)] two or three times daily will give relief. In **syphilitic iritis** where posterior or anterior synechiæ are a frequent complication, early and constant dilatation of the pupil should be secured through the use of solutions of atropine [2 to 4 grains (0.13 to 0.26 Gm.) to 1 ounce (31 Gm.)]. Atropine will relieve the **photophobia** of **acute conjunctivitis** and also that of **chronic conjunctivitis** associated with blepharitis and granular lids, if used in mild solution and not too frequently applied.

In tabetic **optic nerve atrophy**, atropine is always beneficial when injected into the back of the orbit in 1-mgm. ( $\frac{1}{400}$ -grain) amounts. This measure is also diagnostically valuable to ascertain whether an optic atrophy is due to vascular spasm or to actual disease of the optic disk. If the former cause exists, vision improves, and the visual field enlarges within  $\frac{1}{2}$  hour after the injection. C. Abadie (*Presse méd.*, Apr. 19, 1924).

**Internal Uses.—Disorders of the Respiratory Apparatus** are often benefited by belladonna or atropine. In **acute coryza** with excessive flow of thin, watery secretion a small dose of atropine,  $\frac{1}{200}$  grain (0.00033 Gm.), with monobromated camphor, 1 grain (0.065 Gm.), every two or three hours, is often efficient.

Atropine is able to abort a **cold**. The dose required ranges between 0.5 and 1.5 mg. ( $\frac{1}{30}$  and  $\frac{1}{48}$  gr.). This amount of atropine sulphate is dissolved in a glass of water and the

whole sipped in the course of an hour. By the end of an hour or two all symptoms have vanished. If they reappear the next day the dose is repeated. Kohnstamm (Therap. der Gegenwart, Bd. xlvii, Nu. 11, 1907).

In **hay fever**  $\frac{1}{120}$  grain (0.0005 Gm.) of atropine three times a day until slight dryness of the mouth occurs is sometimes very efficient, especially if the fumes of epinephrin inhalant, 1:1000,—applied with an oil atomizer,—or epinephrin ointment are used at the same time.

In **pharyngitis** with increased secretion similar treatment is efficient; if there is much fever 1 drop (0.06 c.c.) of tincture of aconite with 2 drops (0.12 c.c.) of tincture of belladonna may be given every hour or two. **Aphonia**, due to fatigue of the vocal cords, may be removed very speedily by a morning and evening dose [ $\frac{1}{120}$  to  $\frac{1}{80}$  grain (0.0005 to 0.0008 Gm.)] of atropine; **hysterical aphonia** may not infrequently be quickly cured by means of the same treatment.

**Diseases of Alimentary Tract.**—Various gastrointestinal disorders are benefited by belladonna. **Gastric hyperacidity**, when unrelieved by alkaline salts, magnesia, sodium bicarbonate, etc., usually yields when atropine,  $\frac{1}{120}$  grain (0.0005 Gm.), is added to each dose of the latter. **Gastralgia** and the pain of **gastric ulcer** are also relieved by the use of atropine.

Good results are obtained by the use of atropine in the treatment of **gastric ulcer**. The subjective symptoms, especially pain, disappear quickly after beginning the treatment. Hyperacidity and hypersecretion are less quickly influenced. In the writer's cases pyloric stenosis due to cicatricial contraction was

either not at all or only slightly influenced. The writer agrees with the view of Eissinger and Hesse that many ulcer cases are dependent upon an increased vagus tone. This increased vagus tone stimulates the gastric secretion as well as the gastric musculature, and can be diminished by a systematic use of atropine. Schick (Wiener klin. Woch., Bd. xxiii, S. 1229, 1910).

An old formula (Bartholow's) is very efficient in such cases:—

*R Atropine sulph.* ... gr.  $\frac{1}{8}$  (0.013 Gm.).  
*Zinc sulph.* ..... gr. xxx (2 Gm.).  
*Distilled water* ...  $\mathfrak{z}$ j (31 c.c.).—M.

From 3 to 5 drops twice or thrice a day.

In a study of the action of atropine in 28 cases of **gastric disorders** of various kinds, giving 0.001 Gm. ( $\frac{1}{600}$  grain) hypodermically, once a day during 9 days, and in some cases 2 weeks. The writer found that it caused a decrease of gastric secretion, and of acidity, reducing pain and spasmodic contraction, the results corresponding with those of Riegel's experiments on animals. By reducing secretory activity it diminished acidity, thus arresting pylorospasm and pain. Pletneff (Med. Obozrenije, lxxix, No. 3, 1913).

The same combination is very effective in **pyrosis** and **chronic gastric catarrh**. **Vomiting of pregnancy**, **spasmodic vomiting**, or **spasm of the pylorus**, all due to excessive motor activity of the stomach and likewise persistent vomiting in **seasickness**, may all be relieved by the internal administration of  $\frac{1}{120}$  grain (0.0005 Gm.) of atropine sulphate, in water, before meals; if the stomach rebels, the atropine may be given in suppository, or, dissolved in chloroform (1 to 96), it may be used on lint applied to the epigastrium. In **indigestion** with severe colicky pains, also in **mushroom** and **ptomaine poi-**

**soning**, belladonna or atropine affords marked relief.

Habitual **constipation** may be relieved by  $\frac{1}{6}$  to  $\frac{1}{2}$  grain (0.01 to 0.03 Gm.) of the extract in a pill, taken at bedtime.

Added to other purgatives it diminishes their griping action, and, since it increases peristalsis and allays spasm, it increases their efficiency. When there exists a torpor of the lower bowel aloin is a valuable addition. An excellent combination is:—

**R** *Aloin*,

*Ext. nux vomica*,

*Resin podophyllum*,

of each .....  $\frac{1}{2}$  gr. (0.03 Gm.).

*Ext. belladonna* ...  $\frac{1}{4}$  gr. (0.016 Gm.).

Make 2 pills; 1 or 2 at bedtime.

**Pyrosis** may be relieved by atropine ( $\frac{1}{196}$  grain—0.00034 Gm.) combined with 5 drops (0.3 c.c.) of dilute hydrochloric acid, well diluted and taken before meals.

In **lead colic** belladonna, like opium, relieves constipation by removing the intense spasm of the intestinal muscles which causes it.

In **cholera infantum** atropine is sometimes efficient where other means fail. Bailey noted that infants bore atropine well, and gave almost adult doses to children only a few months old, combining the drug with relatively very small doses of morphine: for instance,  $\frac{1}{80}$  grain (0.0008 Gm.) of morphine and  $\frac{1}{150}$  grain (0.0004 Gm.) of atropine, repeated two, three, or four times in twenty-four hours, making the adult dose of atropine. This was found to control the phenomena of cholera infantum, which would have terminated life perhaps in a few hours without. Lauder Brunton also praised atropine in this disorder. In one of his cases, for ex-

ample, in which a child was **collapsed** and apparently dying, a subcutaneous injection of atropine revived her for a time. This was followed by relapse; but another injection was administered, with good results, the child recovering.

**Spasmodic Disorders.**—These are favorably influenced by belladonna. It seems to enhance the analgesic action of the opiates in spasmodic neurosis attended by severe **pain**.

In **pertussis** it is considered one of the most reliable remedies. It is not adapted to all cases, but is most effective in the spasmodic stage and in those cases which are characterized by profuse bronchial secretion. One may employ an aqueous solution of atropine sulphate (1 to 480), giving 2 to 4 drops (0.12 to 0.24 c.c.) at a dose. The tincture of belladonna may be given in doses of from 3 to 5 minims (0.2 to 0.3 c.c.) every three or four hours, stopping when there is a perceptible dilatation of the pupils, or even slight reddening of the skin. The dryness of the throat and mouth may be relieved by small doses of the iodides, by small doses of wine of ipecac or antimonial wine, by occasional small doses of calomel, or by ammonium chloride. Westbrook suggests the following:—

**R** *Tinct. bella-*

*donna* ... 48 to 80 mins. (3 to 5 c.c.).

*Alum* ..... 1 dr. (4 Gm.).

*Syrup of*

*Tolu* .... 1 oz. (31 c.c.).

*Water* .... 2 oz. (62 c.c.).—M.

Of this mixture the child may be given a teaspoonful every two or three hours, day and night, if it is awake. When the spasm is marked and very frequent, the following is used:—

℞ *Tincture of belladonna* .... 72 mins. (4.5 c.c.).  
*Camphorated tincture of opium* ..... 2 to 4 drs. 8 to 16 c.c.).  
*Chloride of ammonium*. 1 dr. (4 Gm.).  
*Bromide of ammonium*. 2 drs. (8 Gm.).  
*Syrup of wild cherry bark*, enough to make ..... 3 oz. (93 c.c.).—M.

Of this a teaspoonful, diluted, is given every two or three hours, night and day, if the child is awake. Forchheimer advocated the use of quinine in conjunction with belladonna.

Another spasmodic disorder in which belladonna, *i.e.*, atropine, has been found helpful is **tetanus**. It is given in small doses, preferably with morphine, at short intervals.

Two cases of **tetanus** in which atropine was employed. In the first case  $\frac{1}{8}$  grain (0.008 Gm.) of morphine combined with  $\frac{1}{300}$  grain (0.0002 Gm.) of atropine was given by the mouth every two hours for three doses and then every four hours. From the first dose the spasms markedly decreased in frequency and severity, and the patient was able to obtain good rest at night. In about four weeks the patient was up and about the house. In addition, small doses of calomel and sodium sulphate were given to keep the bowels open, and the wound was dressed with hot turpentine. The second case was a colored boy 3 years old showing well-marked trismus, though no wound could be found. He had stiffness of the muscles of the body. He was treated similarly, but with smaller doses, and by the beginning of the fourth week all symptoms had disappeared. This treatment was repeated in many cases of tetanus with the same result. Confirmatory of the use of atropine in tetanus is the fact that the govern-

ment veterinary surgeons employed large doses of belladonna with small doses of morphine in treatment of tetanus in animals, and that a fatal result rarely occurred. R. F. Secor (Lancet, May 21, 1910).

In asthma and in the dyspnea which accompanies **emphysema** belladonna gives great relief. During attacks of **asthma**, due largely to reflex spasm and narrowing of the bronchioles, atropine affords relief by paralyzing the motor endings of the vagus, relaxing spasm, and re-establishing thereby free respiration. In severe attacks atropine itself may be injected hypodermically in doses of  $\frac{1}{120}$  to  $\frac{1}{100}$  grain (0.0005 to 0.00065 Gm.) combined with  $\frac{1}{4}$  grain (0.016 Gm.) morphine.

After the paroxysm is relieved, the effect may be prolonged by internal medication. Belladonna leaves may be used by the method of fumigation. The leaves previously dipped in a saturated solution of niter and then dried may be burned in a close apartment, or on a saucer, the fumes being inhaled from a paper funnel covering the same. Pastilles made of belladonna, stramonium, poppy, tobacco, etc., may be used. An excellent formula is Trousseau's for asthmatic cigarettes:—

℞ *Belladonna leaves*.. 5 grs. (0.3 Gm.).  
*Stramonium leaves*,  
*Hyoscyamus leaves*,  
of each ..... 3 grs. (0.2 Gm.).  
*Extract of opium*.  $\frac{1}{8}$  gr. (0.013 Gm.).  
*Cherry-laurel water*. q. s.

The leaves are moistened with a solution of the opium in the cherry-laurel water, and when dry made into a cigarette. Two to four such cigarettes may be smoked daily.

Belladonna is useful in the treatment of **spasmodic cough** and in spas-



modic croup, given between the paroxysms; more rapid measures are needed for the relief of the paroxysm itself. Atropine has also given good results in the initial stage of **influenza** to counteract the catarrhal phenomena of the upper respiratory tract, by restoring the circulatory equilibrium of the respiratory mucosa through its sympathetic supply.

In the treatment of **enuresis**, no single remedy has given such good and uniform results in suitable cases as belladonna. This distressing ailment may be caused by hyperacidity of the urine, relaxed condition of the sphincter vesicæ, or by an irritable condition of the vesical mucous membrane; belladonna gives prompt relief in the two last-named conditions. In male children phimosis, accompanied often by adhesion of the prepuce to the glans penis and retained smegma, is a frequent cause of enuresis; in these circumcision, and not belladonna, is indicated. Again, the presence of ascarides may be sufficient to cause nocturnal incontinence, especially in female infants and children; here again belladonna is of no avail. In suitable cases, as indicated above, atropine, in solution or in tablets, is best suited for internal administration. Beginning with a small dose at bedtime, the dose is gradually increased until systemic effects are produced. It must be remembered that as regards children generally too little of the drug is given. After the relief or cure of incontinence the best results are obtained by continuing the use of the drug for several weeks, in diminishing doses, with an occasional intermission of one to three days, during which time it is not given. This

advice holds good in treating spasmodic disorders generally.

In spasmodic conditions of the rectum or **rectal spasm** associated with **fissure, hemorrhoids, cancer, chronic constipation**, etc., a small suppository (6 to 10 grains—0.39 to 0.65 Gm.), containing from  $\frac{1}{4}$  to  $\frac{1}{2}$  grain (0.016 to 0.032 Gm.) of the extract, introduced well up into the rectum beyond the internal sphincter, gives great relief.

In **intestinal obstruction** or **volvulus** relief sometimes follows elevation of the pelvis on a firm pillow so as to allow gravity to act toward the thorax, especially when combined with starvation, and the use of belladonna and opium (Thomas Bryant). High enemas or bowel flushing enhance the chances of recovery (Stokes).

**Nervous Disorders.**—In **uterine pain** attended by hyperemia, spasm, or **dysmenorrhea**, a larger suppository (30 to 60 grains—1.94 to 3.88 Gm.), containing from  $\frac{1}{2}$  to 1 grain (0.032 to 0.065 Gm.) of the solid extract, may be introduced high up within the vagina and retained by means of a tampon of non-absorbent cotton, at night. In dysmenorrhea the injection of atropine into the cervical canal has also been found helpful.

Report of several cases of **dysmenorrhea** in which injection into the cervical canal of 1 mg. ( $\frac{1}{65}$  gr.) of atropine dissolved in 1 c.c. (15 minims) of water arrested at once the colic spasms in the uterus or prevented their development. If there is no speculum or syringe at hand the same effect can be realized by introducing a small cotton wad moistened with a 1 per cent. solution of atropine and pressing far back against the posterior vault of the vagina. This simple measure has proved effectual in

the writer's experience of fifteen years. Drenkahn (Zeit. f. Gyn., xxxiv, Nu. 47, S. 1529, 1911).

Atropine often gives satisfactory results in **neuralgia**, especially in neuralgia of the trigeminus, and in **sciatica**. In the former, a solution of the drug may be applied externally over the painful area, or instilled within the eyelids, or injected, not subcutaneously, but deeply into the tissues in the neighborhood of the affected nerve-trunk. In sciatica the last method is the best. The largest dose compatible with the safety of the patient must be used (generally  $\frac{1}{400}$  to  $\frac{1}{60}$  grain—0.00065 to 0.0011 Gm.), and decided curative results may be expected if the injection is made straight to the nerve by introducing the hypodermic needle perpendicularly through the overlying tissues. The ointment or plaster of belladonna is a useful application in **neuralgia** of various forms (mammary, intercostal, cervico-dorsal, etc.). A few drops of aconite used to moisten the surface of a belladonna plaster before applying will in most cases increase its efficiency. **Ear-ache**, when neuralgic in character and not produced by pressure of pus against the tympanum, may be relieved by instilling a few drops of a solution of atropine previously warmed. **Periuterine** and dysmenorrheal **neuralgias** are relieved by deep hypodermic injections of atropine in solution. **Muscular cramp** from injuries to the motor nerve is often relieved by atropine injected into the substance of the affected muscle. **Hepatic, intestinal, uterine, and renal colic** may be relieved by hypodermic injections of atropine, but the best results are attained when morphine and atropine are combined. **Vaginismus** has been

relieved by the topical use of pledges of lint wet with a mild solution of atropine.

Atropine is of value in **migraine**. The author gives it for 3 weeks or more to begin with, then in courses of 10 to 14 days at intervals, according to indications. The dosage is 1 to 3 minims (0.06 to 0.2 c.c.) of a 1 per cent. solution of the sulphate 3 times daily after meals. H. D. O'Sullivan (Brit. Med. Jour., Jan. 6, 1923).

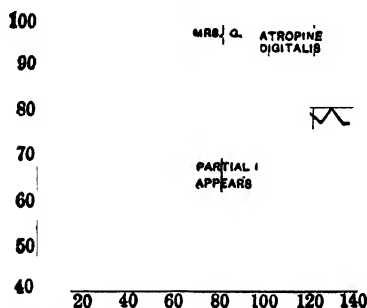
The **insomnia** of mental disorders and of **delirium tremens** may be overcome by the hypodermic injection of atropine when the following indications for its use are present: Coma vigil, great restlessness, weak heart, cold surface, cyanosis, clammy sweat. When there is a condition of hyperemia of the cerebrospinal centers (excitement with elevated pulse rate and increased arterial tension) atropine can only do harm.

Since atropine stimulates the heart and increases the blood-pressure, we find it useful in moderate doses in the **collapse** of fevers, **cholera**, **sunstroke**, and **cardiac syncope**. The dangerous **exhaustion consequent upon colliquative diarrhea** and **internal hemorrhage** indicate the use of atropine. In **congestive chill** due to **malaria**, atropine will sometimes save the patient after all other measures have failed. In this last condition Van Zandt has recommended an initial dose of  $\frac{1}{60}$  grain (0.001 Gm.), followed in 20 minutes by another like dose if no decided effects have been produced. Strychnine sulphate,  $\frac{1}{30}$  or  $\frac{1}{20}$  grain (0.002 or 0.003 Gm.), may be given in addition.

Atropine is useful for the prevention of **shock** during operative procedures with anesthesia. Atropine— $\frac{1}{75}$  to  $\frac{1}{400}$  grain (0.00085 to 0.00065 Gm.)

—may be given before the anesthetic. It may be injected intramuscularly, subcutaneously, or intravenously.

According to Roch and Cottin, while the *atropine diagnostic test* in cases of *bradycardia* cannot be relied on absolutely, yet it furnishes valuable presumptive evidence. It is invariably positive in the cases of bradycardia of nervous-cerebral origin, and negative with bradycardia from heart-block. The test is merely the hypodermic injection of 0.002 Gm. ( $\frac{1}{250}$  grain) of atropine sulphate. The heart-rate is not modified by the drug in case of actual heart disease, while it is accelerated when the myocardium is sound. The reaction becomes evident in 15 minutes, and reaches its maximum in about an hour.



Digitalis and atropine. Upper tracing shows effect of atropine alone; lower tracing, of atropine after a week of digitalis in the same individual. (Rudolf and Bulmer.)

In subjects placed on 1 dram (4 c.c.) of digitalis tincture for a week, with the heart only very slightly slowed, Rudolf and Bulmer (Amer. Jour. Med. Sci., Nov., 1924) found that a single dose of  $\frac{1}{400}$  grain of atropine caused a great exaggeration of the slowing, sometimes down to 40 per minute, and in 1 instance some degree of heart-block. Furthermore, in a case of partial heart-block of long standing,  $\frac{1}{60}$  grain of atropine first increased the block by (central) vagal activity, then decreased the block as the vagal endings became paralyzed. In the same patient,  $\frac{1}{200}$  grain of atropine by mouth thrice daily markedly increased the block, and exercise now did not remove it. Evidently, if atropine is to be given in **partial heart-block** the dose must be large or the block will be increased. In a few

cases of **Graves's disease**, small doses of atropine seemed to slow the heart-rate. In auricular fibrillation, paradoxically, small doses of atropine usually hastened the ventricular rate (probably through reduction of the refractory period).

**Hemorrhagic Disorders.**—In **metrorrhagia**  $\frac{1}{120}$  grain (0.0005 Gm.) twice daily with tamponing is efficient.

In **menorrhagia**, **post-partum hemorrhage**, and **hematemesis** in tuberculosis, the same dose, given hypodermically, but at shorter intervals, has also given good results.

The **night-sweats** of phthisis may be checked by the subcutaneous injection of atropine;  $\frac{1}{60}$  grain (0.0011 Gm.) at bedtime is usually required. The copious perspiration induced by drugs such as pilocarpine, opium, alcohol, and other diaphoretics, may be checked by the use of atropine.

Belladonna is useful in certain skin disorders — **prurigo**, **herpes zoster**, **erythema**, and **eczema**. Sufficiently large doses to maintain a mild physiological action must be used. **Hyperidrosis** and unilateral **sweating** are arrested by the internal or by the local application of the belladonna preparations.

According to Liégeois, extract of belladonna in doses of from  $\frac{2}{13}$  to  $\frac{1}{3}$  grain (0.01 to 0.021 Gm.) is one of the best remedies in chronic **urticaria**, which seems to be attended with an acute edema of the connective tissue of the skin as the result of active vasomotor dilatation.

For the pruritus of **lichen**, Brocq gives fractional doses of tincture of belladonna: 1 to 4 drops *t. i. d.*

Atropine in solution (4 grains to 1 ounce—0.26 to 31 Gm.) may be applied externally in all painful and congested conditions of the skin. Erythematous

dermatitis, erysipelas simplex, pruritus of the vulva, and fissure, etc., may be relieved in this way. The pain of cancerous infiltrations of the skin may be relieved by painting the surface with an atropine solution. The troublesome pruritus of icterus or diabetes is overcome with a flannel compress saturated with a solution of atropine, 1 to 500, covered with a sheet of oiled silk. (Besnier.)

**Antidotal Uses.**—In opium poisoning atropine has been deemed useful, but it is recommended that  $\frac{1}{40}$  grain (0.0016 Gm.) be not exceeded as the total amount given. In the treatment of physostigmine or pilocarpine poisoning, atropine is more directly and effectively antidotal. The tinnitus due to quinine is considerably diminished by adding enough atropine to each dose of quinine to aggregate per day not more than  $\frac{1}{20}$  grain (0.0005 Gm.). It has likewise been found to diminish the secretion of bronchial mucus during ether anesthesia.

A useful property of atropine is its prophylactic and curative action in anaphylactic shock, clearly demonstrated experimentally.

Report of experiments relating to anaphylactoid agents, in which agar solutions were perfused through the lungs of guinea-pigs, causing marked distention due to agar emboli in the pulmonary vessels, which arrested the circulation and closed off the bronchi through mechanical pressure. Atropine, as well as papaverine, was found to antagonize the occlusive effect on the bronchi. Hanzlik and Karsner (Jour. Pharm. and Exper. Therap., xiv, 379 and 449, 1920).

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

## BENZOIN; BENZOIC ACID AND THE BENZOATES.

—Benzoin is a balsamic resin or gum, the concrete juice of the *Styrax benzoin*, a large tree, native of Peru. It occurs in the form of agglutinated lumps or tears, yellowish brown in color, with a milk-white interior. Benzoin has an agreeable balsamic odor, and a slight aromatic taste. It is easily pulverized, the process being apt to excite sneezing. It is almost wholly soluble in 5 parts of moderately warm alcohol and in solutions of the fixed alkalies. Its chief constituents are resin and a volatile oil, benzoic acid (14 to 20 per cent.), and a small proportion of cinnamic acid. Benzoin also contains a principle termed *styracin* (2 to 3 per cent.), and also, in smaller quantities, *vanillin*, *styrol*, and *benzaldehyde* and, in large bulk (75 per cent.), the cinnamic esters of *benzoresinol* and *resinotannol*.

*Benzoic acid* is the most important of the above series, because it forms very soluble and neutral salts, the *benzoates*, with alkalies. It is obtained in various ways: from various benzoin, Asiatic and American; from hippuric acid derived in turn from the urine of horses and cattle; from the oxidation of toluene with nitric acid, etc. The best acid is obtained, however, from Siamese benzoin. It should always, as directed by the U. S. P., give off the agreeable, balsamic, vanilla-like odor of benzoin.

## PREPARATIONS AND DOSES.

—Owing to its property of preventing rancidity, benzoin is added to ointment, forming the benzoinated lard, or *adeps benzoïnatus*—1 per cent.

The tincture of benzoin, or *tinctura benzoini*, may be given in 15 to 30-minim (1 to 2 c.c.) doses. It is also

used as an inhalant, 1 or 2 teaspoonfuls being dropped in  $\frac{1}{2}$  pint of hot water, the steam of which is inhaled through a cone made of a folded towel. Another preparation extensively used in the latter way is:—

The compound tincture of benzoïn, the *tinctura benzoïnî composita* [which contains benzoïn, 10 Gm. ( $2\frac{1}{2}$  drams); aloë, 2 Gm. (30 grs.); storax, 8 Gm. (2 drams); tolu, 4 Gm. (1 dram); alcohol, q. s. ad 100 c.c. ( $3\frac{1}{3}$  ounces)], is used extensively for inhaling purposes in the manner described above, but has also been given internally. Dose, 30 minims to 2 drams (2 to 7.5 c.c.).

Benzoic acid, or *acidum benzoicum*, which occurs in white, pearly plates or needles that become yellowish with age, has an agreeable aromatic odor, but a somewhat pungent taste. It is soluble in 1 to 275 parts of cold water, 1 to 18 of boiling water, 1 to 10 of glycerin, and 1 to 2.3 of alcohol. Its solubility in water is increased by sodium borate. Dose, 5 to 15 grains (0.33 to 1 Gm.). It should not be administered in capsules or cachets, owing to its irritating action on the gastrointestinal mucosa.

Of the many salts of benzoic acid that have been introduced, two are official.

The sodium benzoate, or *sodii benzoas*, which occurs in the form of a white powder or crystals having a sweetish taste and soluble in 1.8 parts of water and in 61 parts of alcohol. Dose, 5 to 30 grains (0.33 to 2.0 Gm.).

The ammonium benzoate, or *ammonii benzoas*, which occurs as a white powder or crystals having a saline, bitter, and acrid taste, soluble in 10 parts of water and in 35.5 parts of alcohol. Dose, 10 to 30 grains (0.66 to 2.0 Gm.).

Both the above salts in solution

should be kept in well-stoppered bottles.

The lithium benzoate, or *lithii benzoas*, N. F., a light, shining, white powder or crystals having a fresh, sweetish taste, soluble in 3 parts of water and 16 parts of alcohol. Dose, 10 to 30 grains (0.66 to 2.0 Gm.).

Benzoic acid lozenges, or *trochisci acidi benzoici*, containing  $\frac{1}{2}$  grain (0.03 Gm.) of benzoic acid each, with a fruit base, are official in the British Pharmacopeia.

#### PHYSIOLOGICAL ACTION.—

Probably the main property of benzoïn as represented by benzoic acid is its antiseptic power. According to Pouchet, this is superior to that of salicylic acid, and even of phenol or carbolic acid, when the benzoic acid employed is free or in solution. A 1:1000 solution suffices to antagonize very actively the pullulation of atmospheric bacteria, while a solution of 2:1000 approximating saturation will sterilize a culture medium; to inhibit cultures in actual development, however, a 20:1000 solution is necessary. The sodium benzoate owes its value to the same property, owing to the fact that it is broken up when absorbed, liberating the benzoic acid. The latter is eliminated as hippuric acid, formed in the kidneys.

When brought into contact with the buccal mucosa, benzoic acid strongly excites it; powdered, it also excites the nasal, conjunctival, buccal, etc., acini, producing hypersecretion. It is probably to the combination of its antiseptic and stimulating actions that benzoic acid, or the preparations in which it enters, owes its therapeutic properties when used locally.

When administered internally, sodium benzoate has been credited with

exerting, besides the antiseptic action above mentioned, the power of enhancing the elimination of wastes. Large doses are known to increase the elimination of urates in the urine, but Söllmann denies the drug diuretic power. It has also been said to increase biliary secretion. Benzoïn and its preparations increase the secretions in the bronchi; hence their use in respiratory tract diseases.

On the heart and circulation, benzoic acid acts much as does salicylic acid, producing, but only in excessive doses, cardiac acceleration, then slowing with lowering of temperature.

**POISONING BY BENZOIN PREPARATIONS.**—A toxic dose of benzoic acid causes vomiting, headache, tinnitus, a sensation of heat in the abdomen, increased frequency followed by slowing of the pulse, diaphoresis, and a marked increase of the bronchial secretion. In animals it causes death by producing bulbo-spinal paralysis with respiratory arrest. Irritation of the gastrointestinal mucosa is very marked, vomiting being sometimes accompanied by gastric hemorrhage. The main action of the toxic dose seems to be spent in the stomach and duodenum, there being no diarrhea. A single dose of 75 grains (5 Gm.) of sodium benzoate has sufficed to cause nausea and vomiting. Marked sweating, salivation, an abundant expectoration of mucus, and hematemesis have also been observed (Pouchet).

Schreiber took in two days about ½ ounce (15 Gm.) of the acid, and experienced only a feeling of abdominal warmth, spreading over the whole body, accompanied by an increase of the pulse rate amounting to 30 beats per minute; also increased excretion of phlegm, with slight disturbances of digestion.

With regard to the possible harm from sodium benzoate in food, Chittenden, Long and Herter, from extensive investigations, concluded that healthy persons may safely consume 0.5 Gm. of benzoate a day in food, provided the latter be not spoiled or unhealthy.

Rarely a patient is encountered in whom the preparations of benzoïn, owing to an idiosyncrasy, produce an eruption, erythema, or even urticaria. These readily pass off, especially if **saline solution enteroclysis** is resorted to to increase the osmotic properties of the blood.

**THERAPEUTICS.**—**Disorders of the Respiratory Tract.**—It is in this class of disorders that the preparations of benzoïn have proven most efficient. When employed early in **acute coryza** sodium benzoate in 10-grain (0.66 Gm.) doses every three hours in a glassful of water, first gargling, then swallowing, often suffices to abort the cold. This treatment is equally valuable in the incipient stages of **tracheobronchitis**, **pharyngitis**, and **laryngitis**, modifying favorably the pain, dysphagia, and inflammation in a short time. Boislinière observed that when 4 to 15 grains (0.25 to 1 Gm.) were given every one or two hours in **follicular tonsillitis** the disorder lasted but twelve to thirty-six hours instead of several days. It is an excellent agent for the various disorders of the singing voice. In **tonsillitis**, as well as in **acute laryngitis**, rapid results are attained by the use of inhalations of the steam of a pint of hot water containing 2 drams (8 c.c.) of the tincture of benzoïn, provided the patient is given at the same time 5 grains (0.3 Gm.) of the benzoate of sodium every two hours. The hot solution of benzoïn is placed in a previously warmed

vessel, and, the latter being covered with a towel folded into a cone, the patient inhales through the upper opening of the latter. In **senile bronchorrhea** ammonium benzoate reduces the sputum and counteracts its fetid odor. Benzoic acid lozenges containing  $\frac{1}{2}$  grain (0.033 Gm.) of benzoic acid each, with a fruit base, are excellent for any of the above disorders.

#### Disorders of the Urinary Tract.—

Owing to the antiseptic and stimulating properties of benzoin, its preparations have been considerably used in this class of cases, especially where the bladder and urethra are involved. Benzoic acid has been thought of value in **chronic cystitis** with fermentation, counteracting the ammoniacal condition of the urine, the irritation and tenesmus, and also the unpleasant odor. It is said also to promote the solution of **gravel** or **ureteral calculi** of whatever nature, and should be given with considerable water. The sodium benzoate has given good results in **urethral irritation**, and even in **gonorrhea**, affording a serviceable adjunct to the local measures employed. In **chronic gout** the lithium benzoate has been thought of some value, owing to its power to promote the elimination of intermediate products of metabolism, uric acid, etc. Benzoic acid is also useful in some forms of **enuresis** in children in 3- to 5-grain (0.2 to 0.3 Gm.) doses.

**Disorders of the Skin.**—The tincture of benzoin is exceedingly valuable as a local application for **abrasions, cuts, frost-bite, bruises, scratches, chapped hands and lips, and fissures**. It is not only antiseptic, but protective, sealing the wound and preventing infection. It does not irritate, as does iodine, nor does it expose the tissues to necrosis, a marked

defect of phenol. Even in **wounds** of a more severe type tincture of benzoin may be employed as a dressing after thoroughly cleansing the lesion and the surrounding tissues. In **anal fissure** it is markedly effective used in the same manner. **Fissured nipples** are equally benefited, the protective covering the tincture affords aiding materially in the healing process.

The tincture serves as a very useful dressing in **foul ulcers** after careful cleansing of the latter with an antiseptic solution and drying. The tincture of benzoin, 2 drams (8 c.c.); glycerin, 2 drams (8 c.c.), and rose water, 4 ounces (120 c.c.), applied as a lotion to **eczema, pityriasis, urticaria**, and **scabies**, proves efficient in most cases, relieving also the itching.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

**BENZOL.**—Benzol, or benzene, chemically  $C_6H_6$ , is the mother substance of the coal-tar series of organic compounds. It should not be confused with *Benzinum purificatum*, U. S. P., or benzine, also known as petroleum ether.

**PHYSIOLOGICAL ACTION.**—When inhaled, benzol vapor is absorbed through the lungs and acts as a narcotic; it produces at first dizziness and headache, then inco-ordination and twitchings, and finally convulsions and coma. When concentrated, the benzol vapor is rapidly toxic.

Taken by mouth in ordinary doses, benzol induces eructations, sometimes dizziness, and occasionally bronchitis. Single doses of 9 to 12 Gm. have been known to cause serious collapse.

Blood changes are readily produced by benzol, however administered, consisting of an apparent destruction of leucocytes in the circulating blood and, after large amounts, marked changes in the bone-marrow, lymph glands, and spleen, with the myeloid tissue particularly affected.

The metabolic disturbances attending benzol administration are shown in the urine by an increase of neutral sulphur, decrease of urea nitrogen, and slight increase of ammonia. The drug is in part oxidized in the body to phenol, catechol, and quinol, and excreted as phenol-sulphates; the remainder is in part excreted unchanged through the lungs and in part completely destroyed.

**POISONING.**—Acute and chronic benzol poisoning are rather common, owing to its use in the arts, in particular as a solvent for rubber. H. J. Cronin (Boston Med. and Surg. Jour., Dec. 18, 1924), in a factory, found the greatest hazards in the "spreader room," in which rolls of cloth were run through a machine that spread a thin coat of rubber compound over its surface, after which the cloth was dried by evaporation of the benzol over hot steam coils.

**Symptoms.**—In the milder *acute* cases, as described by Cronin, the commonest symptoms are headaches, dizziness, gastrointestinal disturbances, weakness, mental dullness and irritability. In severe cases there is respiratory paralysis, cardiac collapse and death. In a fatal case, a buried benzol tank had sprung a leak and an 8-foot trench was dug around it. The victim, assisting in the tightening of a nut at the leak, became dizzy, pale and weak, but after a rest, went at the task again; he then at once collapsed, and died in 10 minutes. Another case, after a few days' rest, had weekly attacks of cardiac distress lasting 3 days for 4 weeks, eventually recovering. On entering the spreader room, Cronin usually became dizzy and felt a constriction of the chest. Several of the 35 employees in the room were anemic, and all were prone to skin infections.

Continued inhalation of benzol vapor sometimes induces *chronic poisoning*, which is marked by purpuric hemorrhages, leucopenia, anemia, and sometimes death, preceded by high fever. Unduly prolonged ingestion of benzol for leukemia may also cause such poisoning. Heim, Agasse-Lafont and Feil, in 30 workers in rubber, observed, along with nervous symptoms, oral hyperemia, benzol odor of the breath, gastric cramps, high blood-pressure, nosebleed and aortic atheroma. Eosinophilic is common, but, according to Teleky and Weiner, a

lymphocytosis exceeding 40 per cent. is the most typical finding; the red cells, hemoglobin and platelets are subnormal.

**Prophylaxis.**—Dilution of concentrated fumes by adequate **ventilation** is the preventive. Over spreader machines there should be a suitable **air exhaust** to remove the hot rising fumes. Port-holes in the wall close to the floor are excellent to remove the heavy descending fumes. Other measures are **rest periods** in fresh air and **rotation of employment** to fresh air occupations.

**Treatment.**—In Cronin's cases this consisted of **iron** for the anemia, **magnesium citrate solution** for the gastric conditions, **acetanilide** for headache, and **ammoniated mercury ointment** and scrupulous cleanliness for the skin infections. Change of occupation was advised.

**THERAPEUTICS.**—The destructive effect of benzol on the leucocytes was utilized in **leukemia** by v. Koranyi and published by him in 1912. The dosage is 5 minims, in capsules, increased to 15 minims, after meals and on retiring. After repeated ingestion a marked drop in the leucocyte count occurs, and the patient's general condition improves. The drug is discontinued when or soon after the leucocytes begin to decline, to avoid toxic effects. The results obtained are not permanent. As pointed out by Brandino, the myeloid and lymphadenoid tissues become aplastic after 15 to 16 injections, but when the action of the drug is suspended, complete regeneration ensues. The cells which prove most resistant are the small lymphocytes and the polyblasts, and these cells initiate the regeneration. S.

**BENZYL BENZOATE.**—Benzyl benzoate is an antispasmodic isolated in 1919 by D. I. Macht. It is a benzyl ester found in some of the balsamic resins, balsam of Peru, cinnamein, tolu, etc., either alone or in combination, and also in the volatile oils of many fragrant flowers.

**ADMINISTRATION.**—Benzyl benzoate is a colorless, oily liquid with a faint aromatic odor, but a bitter, burning taste, which is lasting. It may be given by the mouth in a 20 per cent. alcoholic solution, 15 to 25 drops in cold water being given 3 or 4 times a day for adults. Though



practically non-toxic, larger doses are unnecessary. For infants and children the dose is reduced proportionately. An aromatized suspension is available in the shops, the strength of which is 20 per cent., thus requiring 5 times the above dosage to obtain corresponding effects.

It is available commercially in soluble gelatin globules, each containing 5 minims (0.3 c.c.).

Benzyl benzoate may also be given hypodermically, a 20 per cent. solution in oil being available. The dose ranges from 10 to 60 minims (0.6 to 3.6 c.c.).

Hirschfelder, to avoid the unpleasant taste, gives pure benzyl benzoate, 10 parts; emulsion of acacia, 5 parts; elixir eriodictyi aromaticum (N. F.), 35 parts; dose, 1 teaspoonful. The relief occurs within  $\frac{1}{2}$  hour after taking and is lasting.

**PHYSIOLOGICAL ACTION.**—Jackson, Nielsen and Higgins (Jour. Lab. and Clin. Med., Apr., 1921) obtained marked intestinal relaxation with injections of relatively small amounts of benzyl benzoate and benzyl cinnamate. After repeated injections of large doses of benzyl esters into the blood stream, the arterial blood became very venous in appearance. The coagulation time of this blood was not affected.

**THERAPEUTICS.**—The clinical disorders in which Macht found benzyl benzoate of service were the following: **Excessive peristalsis**, as in **diarrhea** and **dysentery**; **intestinal colic** and **enterospasm**, including the post-operative form; **pylorospasm**, functional, reflex or due to ulcers or tumors; **spastic constipation**; **biliary colic**; **ureteral or renal colic**, **vesical spasm**, **spasmodic pains** due to contractions of the **seminal vesicles**, **uterine colic** which had resisted pessaries, curettage, and other measures; **arterial spasm with hypertension** or **high pressure**, the effects being more lasting than the nitrites, and in some cases more efficient; **bronchial spasm in true asthma**, the latter test having been based upon 200 cases.

J. C. Litzenberg (Jour. Amer. Med. Assoc., Aug. 23, 1919) obtained good results in **dysmenorrhea**.

Musser (N. Y. Med. Jour., Oct. 16, 1920) used benzyl benzoate in 6 cases of **hypertension**, plus a few simple general hygi-

enic directions. In no case did he see any effect, confirming the observations of several colleagues. He also tried it in 2 cases of **angina pectoris**. In several other **painful** or **disagreeable spastic conditions** its action was highly beneficial.

In postoperative or postpartum **bladder distention**, Stater and Vickers (Northwest Med., Jan., 1922) found that benzyl benzoate in doses of 2 to 4 c.c. ( $\frac{1}{2}$  to 1 dram) of the ordinary 20 per cent. alcoholic solution results in micturition within 20 minutes, with subsequent normal control of the bladder.

Later clinical use of the benzyl esters has not afforded convincing support of the earlier recommendations of these compounds, except possibly in **dysmenorrhea**, **angina pectoris** and **intestinal colic**. According to C. M. Gruber and H. H. Shackelford (Jour. of Lab. and Clin. Med., July, 1924), *benzyl benzoate* taken in 30-drop doses 4 times daily for 4 to 18 days has no effect on the blood-pressure in patients with hypertension.

According to D. I. Macht (Jour. of Pharm. and Exp. Ther., July, 1923), *benzyl mandelate*, a new ester of mandelic acid, produces a greater antispasmodic effect than the other benzyl esters, both its alkyl and acid components possessing this action. It markedly relaxed all smooth muscle preparations, especially when in tonic or pronounced contraction. It has no disagreeable taste. Given by mouth in powdered form or capsules in **high blood-pressure**, it caused a definite fall of systolic and diastolic pressure, even in small doses of 1 to 2 grains (0.06 to 0.12 Gm.), with symptomatic relief.

In **spastic constipation** C. D. Aaron (Amer. Jour. Med. Sci., June, 1923) deems benzyl benzoate serviceable in doses of 15 to 30 minims (1 or 2 c.c.) 3 or more times a day.

\* S.

**BERIBERI.**—This term, commonly used for tropical endemic multiple neuritis, is the Cingalese name of the disease, derived by intensive reduplication from "beri"=weakness. The Japanese call it *kakke*.

**DEFINITION.**—An endoepidemic disease or group of diseases, due in

most instances to the excessive consumption of polished white rice, *i.e.*, rice deprived of its pericarp in the process of milling, occurring chiefly in tropical and subtropical countries, characterized by multiple peripheral neuritis, associated in many instances with edema, cardiac weakness, respiratory irregularities, malaise, gastrointestinal disorders, and fever, sometimes terminating in death.

**SYMPTOMS.**—The ever-present and essential feature of this disease is the multiple neuritis, usually of rapid development, and characterized by pain, tenderness, disorder of the tactile sense, abolition of the tendon reflexes, loss of muscular tone, muscular weakness amounting in some instances to complete paralysis, and, at a later period, muscular atrophy. Preceding and accompanying these nervous symptoms, there may be some dyscrasic, scurvy-like state of malnutrition, some form of acute or chronic toxemia, or, most frequently, the clinical symptoms of acute bacterial or plasmodial disease—rise of temperature, headache, furred tongue, anorexia, gastrointestinal disturbance, etc.

In cases in which the phrenic and pneumogastric nerves become involved in the neuritic process, respiratory weakness, rapid pulse, heart failure, edema and anasarca are shown.

Two clinical varieties of the disease are described: the "wet" and the "dry," that is, with edema and without.

In "wet" beriberi the edema appears early and constitutes the characteristic differential symptom. A boggy swelling is noticed first in the lower extremities, increases steadily in amount and in extent, frequently

developing into a general anasarca. The skin becomes pale, watery, and bloodless, the subcutaneous areolar tissue waterlogged, and effusions into serous cavities occur. The respiration is embarrassed, the heart action weak and rapid, arterial tension is low, the carotids pulsate violently, and there is often great precordial distress. A fatal termination within a few days after the first appearance of the disease is not infrequent ("pernicious beriberi").

The sensory, motor, and reflex symptoms of peripheral neuritis may be elicited by examination, but are often inconspicuous in wet beriberi, being masked or overshadowed by the distressing cardiac weakness and anasarca.

Fever, nausea, coated tongue, albuminous urine, intestinal disorder, and other general constitutional symptoms are often present. The onset sometimes occurs with a chill or rigor. Vomiting of blood has been noted.

In favorable cases there is gradual subsidence of the anasarca, disappearance of the heart irregularity and weakness, and of the sensory neuritic symptoms, leaving the patient with some degree of muscular atrophy and paralysis; this latter also slowly subsides, and entire recovery supervenes after weeks or months.

In "dry" beriberi the peripheral neuritic disturbances are more in evidence and the anasarca and cardiac weakness absent. The onset is less acute, the course less rapid, the mortality less.

Pain in the extremities is a prominent and often distressing feature. It may be neuralgic in character, or boring, stinging, burning, and accompanied by formication and by trophic changes in the skin. Tactile anesthesia and other sensory defects are oc-

casionally present. Cramps are sometimes complained of. Tenderness on pressure is usual.

Muscular tonus is lost, muscular weakness or even total paralysis common, the knee-jerks absent, the gait shuffling and unsteady, foot-drop conspicuous.

Muscular atrophy supervenes and may reach an extreme degree in the severer minority of cases, resulting in long-continued paralysis, or even permanent contracture and laming. Trophic joint deformities also occur.

In these "dry" cases, there is often an accompanying dyscrasic state, evidences of malnutrition and toxemia, and disturbance of the stomach. Fever is sometimes shown; malaise and emaciation more frequent.

The course of this form of beriberi extends over weeks in mild forms; months or a year or more in the severe ones.

In both varieties, as in other forms of neuritis, the distribution, extent, severity, duration, and clinical course vary widely at different times and places and in different cases.

The lower extremities are usually first and most affected, although in many instances the nerves of the upper extremities become conspicuously involved. In many instances practically all of the spinal and many of the cranial nerves are attacked. Rarely the arms are more involved than the legs.

The associated general constitutional symptoms likewise vary much in character and severity, being sometimes so slight as to be overlooked, at other times greatly predominating over the symptoms of neuritis.

**DIAGNOSIS.**—The recognition of this disease is easy if it be borne in

mind that the characteristic symptoms are those of multiple neuritis, as above outlined.

If there is pain, tenderness and other sensory disturbances, muscular weakness, loss of muscular tone, muscular atrophy, and absence of the deep reflexes, there is neuritis. If this neuritis is occurring among a number of persons about the same time and place it is properly described as "endemic neuritis," and if endemic multiple neuritis occurs in warm countries, in camps, in hospitals, or on ship-board it is called "beriberi."

Study of the early manifestations of the disease, to ascertain their chronological order, in a series of 100 cases, all adult Siamese males. The earliest symptom noted was always 1 of the 3 following: (a) edema of feet and legs (50 per cent.); (b) numbness or anesthesia of feet (43 per cent.), or (c) epigastric fullness and distress (7 per cent.). The edema appeared first in the feet, next in the legs, and then in the hands. Nearly all patients complained of general weakness. Several stated that swelling of the feet had come and gone before the onset of anesthesia. Cardiac enlargement was found at the first examination in only 15 per cent. of the cases. Hepburn (Brit. Med. Jour., Apr. 3, 1920).

In 109 cases of *infants* from 1 to 12 months old, the author found that aside from the well-known manifestations of vomiting, green stools, rapid pulse, aphonia and absence of reflexes, there are only a few symptoms which unquestionably point to an attack of cardiac beriberi, *viz.*, dyspnea, dilated heart, and enlarged liver. The size of the liver was found to increase in fatal cases and diminish when convalescence set in. T. Suzuki (Nourrisson, May, 1921).

Of 62 cases, 32 revealed abnormal *heart signs*, the commonest being dilatation of the heart, usually more pronounced on the right side, sometimes with evidences of tricuspid regurgita-

tion. The pulse-rate, taken with the patient lying down, varied from 52 to 126 per minute, the average being 84, on admission. The dilatation was usually slight, and disappeared after a short period of rest in bed. Both sides of the heart may be affected. C. A. Sprawson (*Indian Jour. Med. Research*, Jan., 1922).

In beriberi in infants, the writer found by X-ray the volume of the heart 1.5 greater than in other diseases. Considerable cardiac enlargement is present in 75 per cent. of cases of beriberi. Latent beriberi may thus often be demonstrated radiologically—one of the surest means of diagnosis in infants. T. Suzuki (*Nourrisson*, Mar., 1922).

The chief opportunity for the exercise of diagnostic skill is in discovering the cause or causes to which the multiple neuritis is due.

As stated in the definition, beriberi has been found to be due to the use of polished rice. This view has replaced a collection of theories which may, indeed, be characterized as very numerous. A few of these will suffice to illustrate this fact.

**ETIOLOGY.**—The majority of medical men who were brought in contact with endemic neuritis in the tropics became convinced that the disease was primarily bacterial or plasmodial in origin, and much effort was expended by many competent and trained investigators in the attempt to isolate a specific micro-organism—always without success.

It seemed, prior to the unmilled rice phase of the question, that the following were the main causes of beriberi:—

1. Micro-organismic diseases of any kind. Of the known pathogenic organisms, the malarial plasmodium was regarded as the most frequent factor in the production of the disease.

2. Malnutrition from insufficient or improper food.

3. Exposure to dampness and cold, wetting of body surface and subsequent chilling: wading or standing in water, etc.

4. Unhygienic or unfavorable surroundings of any kind, bad ventilation, overcrowding, etc., or anything tending to lower vitality or power of resistance.

5. Use of alcohol.

Any one of the above might cause a multiple neuritis. The first, second, and third, alone or in combination, were most important in causing the endemic form. To them also was attributed that form of multiple neuritis known as beriberi or kakke. All these causes were, however, found to play a secondary rôle, if any, in the genesis of the disease.

The polished rice theory is not of recent discovery, as generally believed. As far back as 1896, Eykman, a Dutch physician, conducted feeding experiments with fowls and found that they would develop polyneuritis when fed on polished rice, but would not do so when given either padi (unhusked rice) or red rice. Polyneuritis of fowls was thought, and still is thought by many, to be analogous to beriberi of man. There has, however, always been in the minds of many a doubt whether these diseases are truly analogous.

The writer dissents from the view of Dutch investigators that beriberi can be identified with the *rice disease* (avitaminosis) of fowls. Among the clinical differences are the following: Anemia is observed in rice disease, not in beriberi. There is lymphopenia in rice disease, but often lymphocytosis in beriberi. Emaciation is common in rice disease; in beriberi no atrophy is seen, except in chronic cases. Hyper-

glycemia is common in rice disease; not in beriberi. In rice disease, one sees, in addition to paresis, jactitation, ataxia and coma; not in beriberi. In beriberi there are cardiac symptoms, with circulatory disturbance, especially venous stasis, which is never found in rice disease. Anorexia and intestinal disorders are common in rice disease, but are not marked in beriberi, except that constipation is common. There are also differences in the pathologic conditions of various organs; among these are the suprarenals, the medullæ of which are sometimes hypertrophied in grave beriberi, while in rice disease hypertrophy of the suprarenal cortices is common. Again, in avitaminosis the amount of vitamin B in the tissues and organs is remarkably decreased; not so in beriberi. Furthermore, a condition similar to experimental rice disease can occur in man—a peculiar form of farinaceous malnutrition (*Mehlnährschaden*) seen in badly nourished infants of the poor, continually fed with solutions of polished rice powder. In 2 such cases the writer found pathologic features exactly coinciding with those of rice disease. He does not maintain, however, that beriberi has nothing to do with a rice diet or with vitamin deficiency in food, nor that vitamin B may not produce good results in preventing or curing beriberi. M. Nagayo (Jour. Amer. Med. Assoc., Oct. 27, 1923).

Vordeman, in 1895-1896, in the prisons of Java fed polished and undermilled rice to different groups of men and succeeded in greatly reducing the number of cases of beriberi by the use of the latter variety.

It remained for Fraser and Stanton (Lancet, Feb. 13, 1909) to prove beyond all reasonable doubt, in a series of experiments on laborers in the Malay peninsula, that beriberi could be absolutely prevented by feeding "cured" (parboiled) rice, and that it would occur in the same places and under the

same conditions when the men were given polished rice. Since these experiments, it has been shown in many countries that the feeding of undermilled rice (which had not been parboiled) has the same beriberi-preventing influence as the use of parboiled rice, and that the beneficial effects of cured rice are due to the adherent pericarp and aleurone layer, and not directly to the process of "curing."

For some years a disease similar to the description of tropical beriberi has been endemic in Newfoundland, according to the writer. During the last 4 years the number of cases occurring annually has been decidedly on the increase. This disease is confined chiefly to the outposts, and is not solely an affliction of the poorer class. About all the cases are among the shoremen, that is men fishing 2 or 3 miles from land in small boats. Gilbert Parker (N. Y. Med. Jour., Aug. 15, 1914).

Explosive outbreaks of the *epidemic dropsy* form of beriberi reported from India. Such outbreaks soon subside, independently of any change in the diet or method of cooking. In 70 cases observed by the writers, the cases occurred simultaneously in separate small groups of persons in limited areas. No evidence could be found of dietary deficiency as an important etiologic factor, though there was a possible association with stored rice, the parboiled rice used by 3 groups having been stored at least a year. Rapid improvement occurred on a modified diet or substitution of rice from a different source and in smaller quantities. Megaw and Bhattacharjee (Indian Med. Gaz., Apr., 1924).

Lack of exercise plays an important part in determining an attack of beriberi where the necessary predisposing conditions of diet exist. All fowls on a diet deficient in vitamin B died in 17 days or less when kept in individual small cages without room for free movement, while of those allowed free

movement none died in less than 31 days. Beriberi is notoriously a disease of confined quarters and fixed diet, as in prisons, asylums, ships, etc. Tailoring, basket-making and mat-weaving do not provide sufficient exercise for the inmates of institutions. D. B. Blacklock (*Brit. Med. Jour.*, June 14, 1924).

The essential substance which is removed by destroying the pericarp of the grain has been found to be the anti-neuritic vitamin B. There is no unanimity of opinion, however, to the effect that lack of this vitamin is the only cause of beriberi. In fact, there are many circumstances which point to the contrary.

From a study of beriberi in the Mesopotamian forces, the writer was led to maintain that it may arise from various causes under different circumstances. One class of cases is not due to a food deficiency but appears to result from an infection. Other cases are due to a vitamin deficiency; this, however, takes a few months to operate in a previously healthy subject and may be called "primary beriberi." In a third class, the syndrome arises apparently from the effect of some depressing influence or secondary infection in a subject previously rendered susceptible to the disease. These cases he classes as "latent beriberi." The clinical appearance is approximately the same in all classes. C. A. Sprawson (*Quarterly Jour. of Med.*, July, 1920).

Vitamin deficiency is rarely the sole cause of the disease. There are factors active in endemic areas, apart from a too exclusive rice dietary, which are absent or of feeble potency in non-endemic areas. While under-milled and parboiled rices are protective against beriberi outside of the endemic zone, they sometimes fail within the latter zone. Among prisoners the disease originates only in the endemic zone, though the diet of prisoners elsewhere is the same. The writer believes in the existence of a poison

which imparts to polyneuritis the characteristics of true beriberi; it is peculiar to certain places or is evolved in persons residing or who have resided for considerable periods in certain places, and its operation is rendered possible by the insufficient intake of a certain vitamin or vitamins in a diet excessively rich in starch and deficient in suitable proteins. Having produced in pigeons, with the rices used in India, 4 distinctive beriberi-like diseases, the writer deems it probable that a similar variety of conditions occurs in man. R. McCarrison (*Brit. Med. Jour.*, Mar. 8, 1924).

Observations indicating that the period of incubation of beriberi is from 92 to 120 days. For protection against the neuritis, the rice used must embody a minimum of approximately 0.5 per cent. of  $P_2O_5$ . The disease developed in 2.79 per cent. of a large number of prisoners fed on polished rice from which the pericarp and the aleuronat layer had been removed. That some as yet unknown etiologic factor, aside from lack of the anti-neuritic vitamin, is involved is indicated by the development of beriberi in persons using hand-ground instead of polished rice; by the increase of the disease during the rainy and decrease in the dry season, and by certain observations pointing to contagion from beriberi cases. A microbic invasion may be the final factor in inducing the disease when the system is undermined by the defective diet. N. van der Walle (*Nederl. Tijd. v. Gen.*, Sept. 20, 1924).

**PATHOLOGY.**—The essential pathological change is parenchymatous degeneration in the nerve filaments of the affected peripheral nerves and atrophy of the muscles to which the motor fibers of these nerves are distributed. In those cases resulting fatally from heart-failure, it is usual to find the heart-wall soft, pale, flabby, and degenerated. In the "wet" cases, general edematous in-

filtration of areolar tissue and effusion into pericardial, pleural, and peritoneal cavities are found.

Other less characteristic morbid changes are met with, dependent upon the nature and severity of the dyscrasic, toxic, or acute germ disease factor which causes or accompanies the neuritis. Gastritis and enteritis with hemorrhage have been seen. Hepatic congestion, parenchymatous hepatitis, acute nephritis, congestion and edema of the lungs, enlargement of the spleen, etc., have been described.

The writers have produced in animals an experimental beriberi by means of a micro-organism, *Bacillus asthenogenes*. In 10 human subjects aged 20 to 40 years who had succumbed to beriberi they found the histologic appearances of the organs similar to those occurring in the experimental beriberi. They deem the bacillus a probable causal factor in man. Bernard and Bablet (C. r. Soc. de biol., Mar. 7, 1925).

An excess of non-protein nitrogen was found in the blood both of beriberi patients and of avitaminous rabbits. Kozawa, Kusunoki and Hosoda (Japan Med. World, Apr. 15, 1925).

**PROGNOSIS.**—The mortality from beriberi varies from 10 to 40 per cent. Death may occur from: 1, The immediate effect of the toxin upon the vital mechanism; 2, failure of the heart action, due to secondary degeneration in pneumogastric nerve and interference with action of heart from pericardial effusion; 3, suffocation from edema of lungs and pleural effusion; 4, exhaustion and occurrence of pneumonia, renal disease, and other complications arising in the course of chronic cases.

In cases which do not terminate fatally, there may be partial paralysis,

muscular atrophy, joint deformities, etc., for a long period, and in rare instances permanently, but the rule is complete recovery after a few weeks or months. Relapses are very common. The use of unpolished rice, however, is rapidly eradicating the disease wherever it can be enforced.

Beriberi may begin slowly or suddenly. When slowly, which is usual, it is preceded by malaise, girdle pains, increasing constipation, and slowly advancing edema of the legs and face. In the rapid form the disease may become full blown over night. The progress of the disease is equally uncertain, some becoming malignant after the disease had existed for several weeks apparently in a mild form. Again, the disease may subside in a week or continue for months. All heart attacks come on suddenly, especially in the paraplegics.

Relapses, although not common, are more often found in patients used to drinking much alcohol. Cases with cardiac involvement need constant attention. In these cases the mortality may range as high as 50 per cent., while in other forms it is as low as 2 per cent. The diagnosis is not difficult when rheumatic pains, pretibial edema and analgesia are present, and the case is known to come from the tropics, where true rheumatism is rare. The knee jerks should always be tested and signs of hyperesthesia of the calf muscles sought. Doyle (N. Y. Med. Jour., Apr. 8, 1916).

While childbearing is not a predisposing cause of beriberi, it seems to make it a much more serious disease. The writer's observations were made among Chinese women. J. A. Hofmann (China Med. Jour., Dec., 1924).

**TREATMENT.**—Important preventive measures are the maintenance of nutrition at normal level; avoidance of exposure, dissipation or excesses; avoidance of infectious tropical dis-

case, and, above all, avoidance of the use of polished rice.

Excellent prophylactic results reported from the use of **unpolished rice** in the Philippine Islands. By way of curative treatment, each patient received daily, in addition to the regular food allowance, 15 grams (4 drams) of **rice polishings**, and improvement was noticed in all except 2 very advanced cases, which subsequently died. Within a month all were pronounced cured. The government drafted a bill providing for the general use of unpolished rice; that is, rice containing at least 4 per cent. of phosphorus as phosphorus pentoxide, and the levying of a tax upon polished rice. Heiser (Jour. Amer. Med. Assoc., Apr. 29, 1911).

The seed of *Phaseolus lunatis*, the **golden butter bean** from Madagascar, is one of the few beans (a cousin of the lima bean of this country) that will grow in all tropical countries, even in the dry season, and a small quantity of these beans eaten every day, with the usual rice ration of tropical peoples, will absolutely prevent beriberi. As there are at a rough calculation 100,000 deaths yearly from beriberi, the importance of a bean that can be grown in the garden of every coolie is obvious.

Beriberi in the Japanese navy was absolutely stopped by a diet of beans. During the Russo-Japanese war the Japanese army reverted to rice only, and there were 40,000 cases of beriberi in the army. C. S. Braddock, Jr. (N. Y. Med. Jour., Apr. 1, 1916).

Large amounts of a **purée of peas** had an unmistakable curative action; 150 Gm. (5 ounces) of the purée 3 times a day were required for this. **Oatmeal** had a similar influence, but 125 Gm. (4½ ounces) 3 times a day were necessary. Europeans did not require quite so much. Pol (Norsk Mag. f. Laeg., Jan., 1916).

Following rules recommended to prevent deficiency diseases: In any institution where bread is the staple article of diet, it should be made

from **whole wheat flour**. Rice used in any quantity should be of the **brown undermilled variety**. **Beans, peas**, or other legumes known to prevent beriberi should be served at least once a week. Canned beans or peas should not be used. Some **fresh vegetable** or **fruit** should be issued at least twice a week, and **barley**, a known preventive of beriberi, should be used in all soups. **Cornmeal** should be of the **yellow** or water-ground variety, *i.e.*, made from the whole grain. **White potatoes** and **fresh meat** should be served at least once a week, preferably once daily, as they prevent scurvy and beriberi. Too exclusive use of canned goods must be avoided. E. B. Vedder (Jour. Amer. Med. Assoc., Nov. 18, 1916).

The **Norwegian gray pea** seems to be effectual in curing ship beriberi as well as Asiatic beriberi, but Pol states that the action of katjang hid-joe, better known as the *Phaseolus radiatus*, of the bean family, is more powerful. Ship beriberi never develops in the acute form sometimes observed with the Asiatic type. With the former, edema gradually extending upward from the ankles is more common than paralysis, and proper food arrests the trouble at once. The European land type of beriberi usually runs a subacute course, and there is always paresis with or without slight edema. A healthy man developed gradual ascending paralysis in 5 or 6 months. Even the larynx was involved. Peas were given cooked and also in the form of a decoction of 2 kg. (70 ounces) boiled down to 1 liter (quart), added to his usual food. After 17 days the paralysis began to subside. Holst (Nederlandsch Tijdsch. v. Geneesk., Sept. 8, 1917).

Addition of **vitamin B** in the diet advocated for preventive purposes. This may be done either by increasing the intake of accessory foods rich in vitamin B if polished rice is taken, or by the substitution for polished rice or half-polished rice, a mixture of rice and wheat, or a mixture of polished



and unpolished rice or beans. Italian millet and corn are also recommended. A most striking reduction of beriberi incidence in the Japanese Army was effected by adoption of a 6:4 rice-wheat mixture. **Improved living conditions** are also important. In the curative treatment, 1 of many **bran** preparations may be used. If over 200 Gm. (6¾ ounces) of bran are taken the effect is immediate. For nervous disturbances **massage** or **electricity** may be employed. K. Ohomori (Japan Med. World, Nov., 1923).

In a period of rice shortage in Malaya, the quantity of rice consumed by coolies was cut down by about ½ and the difference made up largely with flour. Larger amounts of vegetables were also consumed. During this period beriberi was observed to disappear; later, when the rice shortage was ended, it returned. The conclusion reached is that the elimination of beriberi from Malaya does not require complete prohibition of white rice, but merely a restriction of importation of the more highly polished varieties of white rice together with an increase of **vegetables** and **flour** in the diet. C. E. Cobb (Indian Med. Gaz., Aug., 1924).

After the disease has appeared, **removal of the use of polished rice from the diet**, replacing it by unpolished rice or beans, usually suffices to initiate convalescence. If not, symptoms should be dealt with as they develop. The patient should be put at **rest**, a **calomel** purge given, and **liquid diet** ordered. Pain is to be combated by **hot applications**, **coal-tar derivatives**, and, if necessary, **morphine**. Should cardiac weakness persist, **strychnine**, **digitalis**, and **strophanthus** internally and **camphorated oil** or **ether** by hypodermic injection are indicated. **Potassium acetate**, **squills**, **digitalis**, and **saline cathartics** aid in reducing edema in "wet" cases, as do also **vapor baths** and **diaphoretics**, if they

do not debilitate. **Sodium salicylate**, **methylene blue**, continuous small doses of **calomel**, **intestinal antiseptics**, and many other drugs have been recommended. **Quinine** undoubtedly benefits some cases.

The long-continued administration of **strychnine** in gradually increasing doses, until toxic phenomena appear, has been advocated.

External applications, such as the **prolonged warm bath**, **enveloping the limbs in cotton batting**, the **kaolin poultice**, **menthol**, **oil of wintergreen**, and **counterirritants**, give comfort.

At a later period, when acute symptoms have subsided, the use of **massage** and **electric stimulation** to the paralyzed muscles is required.

Removal from damp, ill-ventilated, or otherwise unhygienic surroundings, proper and sufficient food, and removal to a temperate, non-malarial climate are indicated, where possible.

The writer treated 20 cases of human beriberi with autolyzed **brewers' yeast extract**, adults being given from 15 to 40 c.c. (½ ounce to 10 drams) three times a day, and children from 2 to 4 c.c. (½ to 1 dram) every 3 hours. Larger doses did not seem to give better results. A week's treatment seemed to give full relief in mild acute cases. The effect was similar to that produced by the hydrolyzed extract of rice polishings, but seemed weaker. Saleeby (Philippine Jour. of Sci., Jan., 1919).

Writing from Venezuela, in wide sections of which beriberi is one of the greatest scourges, the author recommends that a **change of climate** be advised in every case. **Moderate exercise on foot** and a **nutritious diet** should be ordered, together with **nerve tonics**, **diuretics** if there is a tendency to edema, and **tonics** to the **heart** and **respiratory apparatus**. The paralytic and edematous forms, he finds, get well with mere change of

climate, whereas the fulminating cases are usually promptly fatal. He maintains that beriberi patients should be kept apart from other persons. *Salom* (*Gaceta med. de Caracas*, Apr. 5, 1920).

**Iodine** found useful, 5 drops once daily. In incipient cases 3 doses yielded complete cure. Even in cases with disturbed breathing and heart action, much relief soon followed. *H. W. Ridley* (*Jour. of Trop. Med. and Hyg.*, Mar. 2, 1925).

EUGENE D. BONDURANT,  
Mobile.

**BETANAPHTHOL** is a hydrocarbon prepared from naphthalene. It occurs as a white or yellowish-white powder or in crystalline plates with a faint, phenol-like odor and a pungent taste. It is only slightly soluble in water (1000 parts), freely soluble in alcohol, and readily dissolves in ether, chloroform, or solutions of alkali hydroxides. It is permanent in air.

#### MODE OF ADMINISTRATION.—

Betanaphthol [*Betanaphthol*, U. S. P.] is usually given in capsules, and these, if the drug is given as an intestinal antiseptic, may be coated with keratin. The dose is 2 to 5 grains (0.12 to 0.3 Gm.).

Equal parts of betanaphthol and dried sodium carbonate, thoroughly mixed, can be employed to advantage, the carbonate promoting the solution of the naphthol in water without forming with it a new compound. A 1 per cent. solution of this mixture proved able to kill, in ninety-six hours, dried anthrax spores which resisted the action of 5 per cent. lysol for ten days, and a slightly stronger solution (1.5 per cent.) destroyed them in seventy-two hours. Against typhoid organisms and staphylococci the mixture proved to be about twice as strong as lysol. *Schneider* (*Zeit. f. Hyg. u. Infect.*, Bd. lii, S. 534, 1906).

**PHYSIOLOGICAL ACTION.**—It closely resembles naphthalene in its action. Death is caused by respiratory paralysis in animals, and toxic symptoms have been reported from its use in the human subject. Its external use has caused retinal disturbances.

Case of betanaphthol poisoning during treatment for ankylostomiasis was observed by the writer. In persons with diseases of the kidneys betanaphthol should be used with utmost caution, if at all. *Orme* (*Brit. Med. Jour.*, July 31, 1915).

**THERAPEUTIC USES.**—Its uses are similar to those of naphthalene. It is a good intestinal antiseptic, preventing fermentation and thus flatulence, and is used in gastric or intestinal fermentation, in dilated stomach, and in diarrhea and dysentery. The drug is also a parasiticide and valuable in *uncinariasis*. W.

**BISMUTH.**—Bismuth is a whitish-gray, hard, though brittle, metal, with melting point at 286.3° C., soluble in nitrohydrochloric, nitric, and hot sulphuric acids. It is very commonly contaminated with lead, iron, and copper, together with traces of arsenic, antimony, and tellurium. In the metallic form bismuth is not used in medicine, but its salts, particularly if free from impurities, are of great value.

The garlicky odor sometimes produced in the breath of patients taking the salts of bismuth is due to the presence of the metal tellurium. This fact was first noticed by Sir James Simpson, and was established further in 1875, when specimens of bismuth containing tellurium as an impurity invariably produced in the breath the peculiar odor referred to.

#### PREPARATIONS AND DOSES.

—The official preparations of bismuth are the following:—

Bismuth subnitrate, or *bismuthi subnitratis*, occurs as a heavy, white, microcrystalline powder, which is almost odorless and tasteless. It is nearly insoluble in water, insoluble in alcohol, but soluble in nitric or hydrochloric acid. Dose, 15 grains (1 Gm.).

Bismuth subcarbonate, or *bismuthi*

*subcarbonas*, occurs as a white or yellowish-white, tasteless and odorless powder. It is insoluble in water or alcohol, but readily soluble in nitric or hydrochloric acid with effervescence. Dose, 15 grains (1 Gm.).

. Bismuth subsalicylate, or *bismuthi subsalicylas*, a white, amorphous, odorless and tasteless powder, almost insoluble in water, decomposed by alcohol, ether, and acids with liberation of the salicylic acid. Dose, 15 grains (1 Gm.).

Bismuth subgallate, or *bismuthi subgallas* (also known as *dermatol*), an amorphous, yellow, odorless and tasteless powder. It is insoluble in water and alcohol, but soluble, with decomposition, in heated hydrochloric, nitric, and sulphuric acids, and dissolved by alkalies. Dose, 15 grains (1 Gm.).

Several unofficial compounds are used, apart from the numerous preparations employed in syphilis:—

Bismuth betanaphthol, or *bismuthi betanaphtholas* [U. S. P. IX], is a compound containing about 15 per cent. of betanaphthol and yielding, on ignition, about 75 per cent. of bismuth oxide. It is a buff-colored to grayish brown, tasteless powder, nearly insoluble in water or alcohol. Dose, 5 to 15 grains (0.3 to 1 Gm.).

Bismuth and ammonium citrate, or *bismuthi et ammonii citras* [U. S. P. IX], translucent scales with a slightly metallic and acidulous taste. It is very soluble in water, but slightly so in alcohol. It is affected by light and air, and should, therefore, be kept in dark, well-stoppered bottles. Dose, 1 to 5 grains (0.065 to 0.3 Gm.).

Bismuth citrate, or *bismuthi citras*, a white, amorphous, odorless and tasteless powder. It is insoluble in water or alcohol, but soluble in solu-

tions of the alkaline citrates and ammonia water. Dose, 3 to 10 grains (0.2 to 0.6 Gm.).

Bismuth tribromphenolate (also known as *xeroform*) contains 50 per cent. of bismuth oxide and occurs as a yellow, nearly odorless and tasteless powder. It is insoluble in water. Dose, 10 to 15 grains (0.6 to 1 Gm.).

Bismuth nosophenate (also known as *eudoxin*), a bismuth salt of tetraiodophenolphthalein. It is a reddish-brown, odorless and tasteless powder, insoluble in water. Dose, 5 to 15 grains (0.3 to 1 Gm.).

**Preparations Used in Syphilis.**—The introduction of bismuth in the treatment of syphilis led to the production of many new preparations intended for administration by injection. Only the most important of these can be mentioned here. The compound originally used by Sazerac and Levaditi is known as *sodium and potassium tartrobismuthate*, and contains 50 per cent. of bismuth. In a more recent method of preparation, however, additional washing and drying of the salt have been availed of, raising its bismuth content to 55 per cent. *Trepol* is a 10 per cent. suspension of the tartrobismuthate in olive oil, and is intended for intramuscular injection.

A. Catzeffis (Ann. des mal. vén. Apr., 1924) prefers *quinine iodobismuthate* (*quinby*), having found trepol painful and at times productive of dyspnea and albuminuria. The iodobismuthate, employed after mercury or neoarsphenamin, or alone in chancre and secondary lesions, was itself not always well borne, causing marked dental pain in 2 cases and albuminuria and pyelitis in 1 each. In the young and delicate, 0.1 Gm. is used as the initial dose. The needle employed in injecting should not have been used for loading the syringe. The injection is given slowly, and the skin pinched up as the needle is withdrawn. Rest for 30 minutes should follow the injection. Boesch usually injected trepol or quinby every 3 to 5 days in respective doses of 2 and 3 c.c. to a total of 20 injections.

*Neotrepol*, likewise first prepared by Sazerac and Levaditi, is based on the pro-

duction of bismuth metal in a fine state of subdivision by the reduction of a bismuth salt. The bismuth is held in suspension in a sterile isotonic solution. The therapeutic dose is 0.15 to 0.2 Gm. of the drug, given twice weekly in a series of 10 to 12 injections. Schwartz and Levin, among others, have reported good results with this preparation, injecting 0.5 to 2 c.c. of the solution every 4 to 7 days, deep down into the muscle, with care to avoid escape of any of it into the fatty tissue. It was found well tolerated, pain being practically *nil* and buccal symptoms rare. Sutton has reported the only case on record of abscess following injection of this preparation.

Cysts and nodules are not uncommon following the deep intramuscular injection of the salts of heavy metals, but the author's case of abscess is the first, so far as is known, resulting from an injection of bismuth metal. The patient was a woman aged 18, infected 4 weeks previously. After her third intravenous injection of sulpharsphenamin she was given bi-weekly injections of neotrepol deep in the gluteal muscles. After the sixth of these, she complained of much pain. In the right buttock was a tender, hot, red mass resembling a large grapefruit. She was advised to take hot sitz-baths twice daily and to make hot applications in the interim. Small doses of codeine were given. Twenty-four hours later a fluctuating abscess had formed, with definite pointing. This was incised, and chocolate colored pus discharged. The abscess drained freely for several days. The X-ray revealed no bismuth deposits in the muscles. J. C. Sutton (Jour. Amer. Med. Assoc., Jan. 30, 1926).

Shivers (Arch of Derm. and Syph., Oct., 1924) uses *potassium bismuth tartrate* with butyn (Dermat. Research Lab.), generally in weekly intragluteal doses of 0.1 Gm., or in some cases with more active lesions, 0.2 Gm. Two courses each totalling 2 Gm. are given with an intervening rest period of 4 weeks, and finally a 3d course after a longer interval. Usually no local tenderness occurred, and there were no infections.

The *oxybenzoic acid* compound of *bismuth*

(*bismogenol*) has been successfully used by Ahlswede and Busch in primary syphilis with heart disease contraindicating arsphenamin. Fifteen injections of 1 c.c. were given at intervals of 2 or 3 days. Bismogenol is a 10 per cent. suspension of the compound in oil. The compound itself contains approximately 60 per cent. of metallic bismuth.

Lomholt recommends a *suspension of bismuth in glycerin*, made up as follows: Precipitated *bismuth hydroxide*, 10 Gm.; glycerin, 5 c.c.; distilled water, to make 50 c.c.. It must be shaken just before use. The bismuth hydroxide soon renders it sterile. The dosage is 1 c.c. once weekly. Absorption is much more rapid than with the oily preparations. But little local pain is produced.

Though attempted by some observers, intravenous administration of bismuth has, in general, been deemed inadvisable.

A 10 per cent. *bismuth ointment* known as bismophan was found useful by Oelze in the treatment of broad rectal condylomas, papules and oral mucous patches. The bismuth dosage used was the same as that of mercury. No pronounced effect on the serum reactions was noted.

Injections of metallic bismuth are dangerous, and if persisted in will lead to cumulative absorption and possibly even fatal results. The same is probably true, to a less extent, of bismuth oleate and salicylate. Their use should be replaced by one of the more soluble bismuth salts—perhaps the potassium-bismuth tartrate preparations, injected intragluteally once a week. Even then, the patient should be observed closely. Injection of insoluble bismuth salts twice weekly is open to question; only a small amount will be absorbed, and too frequent deposits may be dangerous. Cole, Farmer and Miskdjian (Arch. of Derm. and Syph., Feb., 1926).

#### PHYSIOLOGICAL ACTION.—

Applied to excoriated or ulcerated surfaces, the salts of bismuth exert an astringent and sedative action, but some of the salts, notably the subnitrate, salicylate, betanaphtholate, and

nosophenate, are antiseptic. They also cause drying of the secretions and form a protective covering over the wound, which thus heals under a scab that the bismuth has rendered aseptic. They have been used extensively, therefore, for the external treatment of wounds, but, as shown below, this may be followed by absorption and poisoning.

The same properties have rendered bismuth preparations, especially the subnitrate, extremely valuable in the treatment of gastric and intestinal disorders. They tend to check the gastrointestinal putrefaction of proteids, and thus prevent not only the local catarrhal disorders of the mucosa of the alimentary tract to which the products of putrefaction, including acetone and diacetic acid, give rise, but also the absorption of these acids and the resulting autointoxication. Moreover, being insoluble in the intestinal juices, they coat the mucosa and absorb what free acids are formed, thus protecting the intestinal surfaces in two ways. In addition, they neutralize the acidity of the intestinal contents and precipitate the hydrogen sulphide. Unfortunately, most bismuth salts tend to constipate by checking peristalsis, though this action becomes useful in the treatment of diarrhea and vomiting.

**BISMUTH POISONING.**—The prevailing view that bismuth subnitrate may be used with great freedom, both externally and internally, has been the cause of many cases of poisoning. Three classes of cases should be recognized: (1) those in which the drug is administered by the stomach or rectum as a remedy, (2) where used as a surgical therapeutic

agent, powder, paste, etc., or (3) as an aid to facilitate the X-ray examination of the gastrointestinal tract.

**Poisoning in the Course of Internal Medication.**—The statements of some books that pure bismuth can be taken "without injury in indefinite quantity," or that "two or three drams a day may be given to a child a year old," for example, are dangerous advice. As shown by clinical experience, even  $7\frac{1}{2}$  to 15 grains (0.5 to 1 Gm.) repeated every two hours have sufficed to produce cyanosis in infants, with somnolence, and a marked garlicky odor of the breath. When the doses are larger, there appear: black- or slate- colored discoloration of the edge of the gums and of the mucosa of the mouth and gastrointestinal canal, stomatitis, gingivitis, headache, abdominal pains, vomiting and diarrhea, dysphagia, fever, delirium, deepening of the cyanosis with dyspnea and hypothermia, diminution in the amount of urine, methemoglobinuria, albuminuria, nephritis, hiccough, collapse, and even death. Where an idiosyncrasy exists in the adult 15 to 20 grains (1 to 1.3 Gm.) sufficed to produce toxic phenomena, including an eruption resembling that of scarlatina (Dubreuilh). Mathieu has observed under very large doses in adults a pigmentation resembling the chloasma of pregnant women.

Acute poisoning by subnitrate of bismuth in a woman aged 22 years suffering from tuberculous stenosis of the small intestine. She had been in the habit of taking subnitrate of bismuth in doses of from 15 to 30 grams. She developed symptoms much like those of methemoglobinemia, such as difficulty of the respiration, convulsions, a subnormal

temperature, and intense cyanosis. The patient was in a very grave condition for two days, but, nevertheless, recovered. Bensaude and Rivet (Lancet, Feb. 20, 1909).

Subcutaneous injections have been found to produce stomatitis with erosions and sloughing, albuminuria, enteritis with bloody stools, and slight hepatic congestion.

Rectal injections of bismuth subnitrate in emulsion are even more dangerous than when the salt is administered orally.

All these toxic phenomena having been obtained with the subnitrate, Böhme ascribed them to the nitrites produced and absorbed from this salt. The feces were found capable of reducing nitrates to nitrites, a process facilitated by pronounced bacterial activity. Poisoning is of course liable to occur, therefore, in subjects of all ages, but especially in children suffering from intestinal putrefaction. This form of intoxication is admittedly not due to the metal bismuth, but to the special salt bismuth subnitrate. In the light of this view it may be preferable to employ a different salt, such as the carbonate, when large doses are required. Lewin ascribed the toxic effects to the absorption of bismuth as a sulphide, but Böhme's view has been sustained by other investigators.

**Poisoning in Syphilis.**—The commonest toxic effect relates to the mouth, ranging from a simple *pigmentation of the gums* to *gingivitis* and *ulcerative stomatitis*. Hudelo, Bordet, and Boulanger-Pilet noted oral manifestations in each of 14 syphilitics to whom they gave 0.2 to 0.3 Gm. of potassium and sodium tartrobismuthate in oily suspension intramuscularly every *three* days. All of them showed a *dark blue line* at the gum margins, and some had dark spots on the inner surfaces of the cheeks. In 5 cases there were also superficial ulcerations on the gums or cheeks, all recovering, how-

ever, in 10 or 15 days. Bismuth stomatitis differs from mercurial stomatitis in that the ulcerations develop suddenly, the tongue is relatively unaffected, there is less salivation, and the blue line is constantly present.

According to Armuzzi and Stempel, the stomatitis is due to the precipitation of bismuth sulphide by  $H_2S$  and its mechanically obstructive action in the finer blood-vessels as well as its destructive effect on their endothelium. Upon these injuries bacterial invasion is superimposed. Stomatitis often depends upon the presence of decayed teeth. With the black line on the gums there may be enlarged, black papillæ on the dorsum of the tongue. According to Hudelo and Rabut, stomatitis is much commoner when the bismuth is given as a tartrobismuthate than when as an oxide or combined with quinine.

Other possible effects of bismuth are acute odontalgia and salivation. There is usually little disturbance of the alimentary tract, although the appetite may be impaired and in rare instances there develop severe attacks of gastric pain, with or without fever and vomiting. Jaundice and attendant hemorrhagic manifestations are very exceptional. Hudelo and Rabut noted only 4 instances of albuminuria in 10,000 injections. Skin eruptions are uncommon and devoid of seriousness. Lassitude is a usual condition during and after the treatment. Fever and pain in the joints and muscles are less frequent. Occasionally are met with such nervous symptoms as dizziness, nitritoid crises, headache and hemiparesis or paresis of the lower extremities.

After an intramuscular injection, bismuth can be traced in the muscle with the X-ray. Veillet and others have advised X-ray examination of the area of injection to make certain of complete absorption of the bismuth before a second course of injections is begun. According to Ahlswede and Busch, the risk of bismuth accumulation is small—particularly with the oxybenzoic acid compound—provided the initial dose is carefully studied and dosage thereafter increased gradually under guidance of the blood picture. A sudden decrease of the white cells, especially the lymphocytes, or a sudden drop in the red cells calls for immediate cessation of the treatment and rest.

Pulawski has reported a fatal case show-

ing the extreme importance of careful and thorough observation of the mouth during treatment. In this case a second course of injections had been begun in spite of the recent appearance of ulceration and pain in the tongue.

In regard to the effect of bismuth on the kidneys, varying opinions have been expressed. Engelhardt, summarizing reports on the secondary effects of bismuth, found harmful effects on these organs mentioned in nearly all. Most writers, however, did not regard these effects as serious, actual nephritis very rarely resulting.

#### **Poisoning when Used Locally.—**

The local application of bismuth subnitrate in the form of powder to burns, excoriated surfaces, etc., or in that of emulsion or paste into cold abscesses, fissures, fistulas, etc., has also given rise to untoward effects followed in some instances by death. Sprinkled over burns of the second or third degrees, for example, the subnitrate forms a scab-like layer which protects the lesion well enough, but which, however, does not prevent the gradual absorption of the drug or its components into the blood. Gingivitis with the slate-colored line and stomatitis characterized by more or less pain and swelling may then appear, followed by the above-described toxic phenomena and even death if the quantity absorbed be sufficiently large.

Case of a delicate woman who was treated with a 10 per cent. bismuth salve for a burn. After a few weeks she began to show signs of bismuth poisoning and a nephritis. The case ended fatally. At the autopsy, the mucous membrane of the entire colon was found to be stained black. The cause of the poisoning in this case is ascribed by the author to the extensive areas on the body deprived of cuticle to which the salve was applied. Mahne (Berl. klin. Woch., Feb. 27, 1905).

A review of the literature showed that up to 1916 there had been 43 reported cases of intoxication, 13 of them fatal, following the local application of bismuth to granulating surfaces. W. H. Higgins (Jour. Amer. Med. Assoc., Feb. 26, 1916).

The introduction of bismuth paste by Beck for the treatment mainly of tuberculous sinuses, infected abscesses in Pott's disease, etc., was followed by many toxic cases. The earliest symptom of the chronic form of poisoning, due to the slow and prolonged absorption of bismuth by a suppurating surface, is a pale, livid tint of the skin. This is followed by an eruption of small, bluish ulcers on the gums. The further progress of the poisoning is marked by nausea, headache, vomiting, and albuminuria. In advanced cases the ulceration of the gums increases, and the patient becomes emaciated and gradually succumbs.

Beck, who in his own practice observed cases of the kind, stated that the bad results can be prevented by constantly **looking out for** the appearance of the **early signs** of the poisoning, and if any of these be manifested by injecting into the cavity still occupied by the bismuth paste some warm and **sterilized olive oil**, which is allowed to remain 12 to 24 hours, *i.e.*, until it has formed an emulsion that can be removed by aspiration.

Case of rather severe bismuth poisoning occurring from the injection of about 45 c.c. of Beck's paste into a discharging sinus. **Irrigation of the sinus with warm olive oil** removed the bismuth and patient soon made a good recovery, except that some pigmentation of the gums and tongue persisted. Freilich (Jour. Amer. Med. Assoc., Jan. 13, 1917).

Beck states that the use of bismuth paste is contraindicated in cases of

acute suppuration, particularly empyema, as absorption so readily occurs on the fresh inner surface of the suppurating pleura. On the other hand, in old abscess cavities with thick and fibrous walls with much diminished capacity for absorption, the paste may be applied with but slight risk. The maximum strength of the paste used is 33 per cent. When the secretion becomes sterile, the paste is withdrawn and replaced either by a 10 per cent. paste or by sterilized vaselin.

**Poisoning from Use in X-ray Examination.**—Since arsenic-free bismuth has been available, the subnitrate has been extensively used to facilitate X-ray examinations of the alimentary tract. Unfortunately, large quantities are necessary, and many cases of poisoning have occurred, absorption taking place from the intestine after decomposition of the salt. The symptoms are those already described; they appear from one to four hours after the use of the salt. Nausea, vomiting, marked cyanosis, prostration, and rapid respiration may all occur, last several hours, and the case proceed to recovery, especially if the poison is removed. In unfavorable cases methemoglobinemia and the other symptoms described appear in rapid succession until death occurs. The completely insoluble barium sulphate having, as is well known, largely replaced bismuth in X-ray work, the risks from the latter no longer figure prominently in clinical medicine.

Case of fatal poisoning following injection of bismuth paste into the knee because of a sinus after trauma.

A 4-year-old child was given a dram (4 Gm.) of bismuth subnitrate in a starch enema because of colitis. Twelve hours later she became nauseated, very

cyanosed, with pulse small and weak, and partial coma supervened. The blood was very dark. The colon was irrigated repeatedly and injections of camphor given hypodermically, and within 24 hours she was much better. A man, aged 50, had been given an ounce (30 Gm.) of bismuth subnitrate in milk for X-ray gastric examination. During the night symptoms of poisoning appeared, and persisted for 3 days. J. Phillips (Cleveland Med. Jour., June, 1917).

**TREATMENT OF BISMUTH POISONING.**—Prophylaxis requires that the doses mentioned at the beginning of this article should be approximated and adjustment made to the age of the patient. The surgical use of bismuth is subject to the same rules, unless care be taken not to leave it on or in the tissues sufficiently long to permit the absorption of enough bismuth to bring on toxic symptoms. If any appear, the drug should at once be removed by prolonged warm bathing of the encrusted surface or injection of **warm vaselin** and **aspiration** when dealing with cavities.

For X-ray examination, the stomach or rectum should be carefully washed out and all bismuth removed as soon as the skiagraphic exposure is terminated, following up the colonic irrigation by a saline purgative.

As regards bismuth in *syphilis*, prophylaxis consists in denying such treatment to patients with many carious teeth, gingivitis, renal insufficiency, distinct hepatic insufficiency or poor general condition. It is not contraindicated by traces of albumin. Temporary suspension of treatment is indicated by increase of albumin or by gingivitis, jaundice or immediate skin eruptions. In late eruptions or ulcerative stomatitis bismuth treatment should be abandoned.



As a rule, no more than 0.2 to 0.25 Gm. of bismuth oxide or 0.3 to 0.4 Gm. of quinobismuth twice weekly should be given, and a rest period of at least a month should elapse after a series of 18 to 24 injections has been made (Hudelo and Rabut).

In the average patient stomatitis may be avoided by proper **dental supervision** and a **hydrogen peroxide mouth-wash**. For actual stomatitis Fournier and Guénôt advocate, aside from the peroxide, **methylene blue** or local **arsenical applications**, together with lengthening of the intervals between doses and reduction of dosage. The favorable results from local **arsphenamin** application in healing bismuth ulcers are ascribed by Azoulay to the fact that Vincent's spirilla and fusiform bacilli are always to be found in these ulcers after an initial stage of polybacterial invasion.

According to Semon, the symptoms of bismuth stomatitis are rapidly relieved by intravenous injections of 0.45 to 0.6 Gm. (7 to 9 grains) of **sodium thio-sulphate** in 5 c.c. (80 minims) of water on alternate days.

**THERAPEUTICS.**—The most important therapeutic application of bismuth has been in **gastrointestinal disorders**, ever since Trousseau demonstrated its great value in these affections. While the use of the massive doses recommended by various authors has clearly shown that bismuth is not free of toxic effects, thus somewhat lessening its use, the fact remains that in judicious doses it is worthy of the greatest confidence, particularly in the various forms of dyspepsia.

Bismuth is particularly valuable in all cases of painful **gastritis** (Hayem). It acts favorably on **gastrorrhagia**

and it also reduces **abnormal fermentations**. The improvement is prompt and the relief very marked in all varieties of cases of **gastric pain** (early or late pains, cramps, burnings, intolerable pains, sensations of weight, uneasy feelings, unseasonable pangs of hunger, etc.). In severe cases it may be impossible to give the bismuth at the beginning; but as soon as the acute period has passed, it can be exhibited with the most favorable results. Its calming effects are obtained generally during the second or third day of treatment, but more frequently not until the sixth day. In **nervous dyspepsias**, and in gastric crises of central origin, only temporary relief can be looked for. In **gastric ulcer**, its use has become classic; it relieves pain, stops reflex irritation, and its protective properties favor rapid healing of the lesion. Even in **cancer of the stomach**, the beneficial effects of bismuth are sometimes remarkable in relieving pain, but they are only temporary, and the patients are obliged to take it constantly.

[It is a question whether the analgesic property of bismuth subnitrate is not due to the poisonous effects of liberated nitrites, *i.e.*, to a poisonous action. This is suggested by the facts that large doses are alone effective, and that the subnitrate of all the bismuth salts alone relieves pain to any material degree. The physiological action of the nitrites being to dilate the arterioles throughout the entire body, the general blood-pressure is relieved and the congestion of the painful area likewise, thus diminishing temporarily its sensitiveness. C. E. DE M. S.]

If it becomes necessary to administer more than 40 grains (2.6 Gm.) three times a day—suspended in water—to relieve the pain of gastric cancer it is preferable not to increase

the dose, but add thereto either codeine, morphine, or cocaine.

**Dyspepsia** attended with hyperacidity, irritable stomach, and **gastric cancer** is often happily influenced by the following powder:—

R. *Subnitrate of bismuth*,  
*Carbonate of magnesium* . . . . of each 5 grs. (0.33 Gm.).  
*Morphine sulphate* ..  $\frac{1}{12}$  gr. (0.005 Gm.).  
 M. For 1 powder.

**Acute or chronic diarrheas** are often relieved by bismuth. A dose of castor oil in advance of bismuth subnitrate is of value in removing any possible cause of irritation.

In severe **infantile diarrhea** it is best to commence with a dose of 3 to 5 grains (0.2 to 0.33 Gm.); it is then possible to dispense entirely with opium in many instances. The drug can be administered to children in a mixture with glycerin and water, to be shaken before ingestion. The powder form should be avoided, as it is liable to produce irritation of the gastrointestinal mucous membrane.

Many cases of **vomiting**, even the **vomiting of pregnancy**, will usually yield to the administration of 10-grain doses of one or other of the bismuth salts. It is not always tolerated by the stomach when given in larger doses. This drawback may be in a measure obviated when necessary by combining it with an aromatic powder or magnesia. The formula given above under "dyspepsia" is of great value in such cases.

Lion recommends that, in cases of **pulmonary tuberculosis** with coughing and vomiting after meals, 20 grams (300 grains) of bismuth subnitrate be given in two-thirds of a glassful of water one hour before a meal. Usually after the very first dose the vomiting is entirely pre-

vented, and if the treatment be kept up ten or twelve days it will cease permanently. Occasionally the cough provoked by taking food persists, but it is no longer followed by vomiting. H. Paillard (*Progrès méd.*, Jan. 27, 1912).

[The above abstract illustrates the dangerous recklessness with which bismuth is used owing to the prevailing belief that it is a harmless agent. Such enormous doses are not necessary to prevent the above form of emesis. C. E. DE M. S.]

The color of the stools is changed to a blackish or slate-like hue when bismuth is administered, but this need give rise to no anxiety.

The salicylate of bismuth, the dose of which is smaller, is very efficient in **infantile diarrhea** in doses of 1 to 2 grains (0.065 to 0.13 Gm.). It has also been used in the diarrhea of **typhoid fever**, but the betanaphtholate is generally preferred, owing to its greater antiseptic activity. Both salts may be administered together, however, with advantage, according to some authors. The double salt of bismuth and ammonium citrate is also valuable in **acute and chronic diarrhea**. This applies also to a marked degree to bismuth subgallate, but in 5- to 10-grain (0.33 to 0.66 Gm.) doses three times daily.

**Local Use of Bismuth Preparations.**—The toxic effects of bismuth subnitrate when applied as a dusting powder to exposed surfaces have somewhat reduced the use of bismuth salts in surgical disorders, but if it is remembered that it is the subnitrate that has given rise to the untoward effects reported it is only necessary to limit its use to small **excoriations, ulcers, burns**, etc., to avoid such effects. Or, the subcarbonate may be

used instead. The tribromophenolbismuth (xeroform) has been found to replace iodoform in **infected wounds, ulcers, and in uterine erosions.** The subnitrate or subcarbonate of bismuth is extensively used also as dusting powder in the treatment of various skin disorders, especially **erythema, vesicular eczema, acne, and intertrigo.**

For the treatment of **fistula** of various kinds, those, for instance, following **empyema, mastoid disease, tuberculous abscesses, tuberculosis of the spine and joints, resection, etc.,** Emil G. Beck's bismuth paste has been extensively used with excellent results when the lesions were not too extensive or too far advanced. The subnitrate having caused poisoning in many cases, as we have seen, the subcarbonate may be used instead, though it does not entirely avert the untoward effects, unless the quantity recommended is somewhat reduced. J. C. Beck's main mixtures, used in 319 cases, are as follows: (1) A paste containing 33 parts of bismuth subnitrate and 67 parts vaselin, which is used principally in the localities where the idea is to cover rather than distend and as a local treatment of the nasal mucosa in **hypertrophic rhinitis.** (2) A paste containing 30 parts bismuth to 60 of vaselin and 5 parts each of white wax and paraffin, which is of almost universal application, except for filling the defect of simple **mastoid operation,** where a paste containing less vaselin and double the above amount of white wax and paraffin is used. (3) A still stiffer paste of 30 parts bismuth, 35 parts vaselin, 25 parts paraffin, and 10 parts white wax, used only in the radical **frontal sinus operation** to act as a plug. The syringe used is a powerful instrument

working on the thread principle. The flexible tube is essential and must be of metal, as rubber distends and soon breaks. If any sign of poisoning appears the paste should be softened with warm vaselin and aspirated, and the cavity washed out.

Failures of bismuth paste to cure are due to the following causes: 1. The bismuth is not sufficiently incorporated into the petrolatum, leaving large masses of pure bismuth. 2. Water accidentally gets in and makes a mass like curdled milk. 3. The mixture is not heated sufficiently before injection. 4. Improper instruments are used. 5. Undue force is used; the paste must be forced in very slowly. 6. The sinus is incompletely filled. 7. The sinus is injected too frequently. 8. The patient is allowed to dress his own wounds. Two bacterial examinations should be made, one before and one after injection; if the second is negative, one must not repeat the injection. Finally, the wound should be dressed daily. E. G. Beck (N. Y. Med. Jour., June 17, 1916).

Brandes passes a rubber tube or catheter into the fistula to its bottom and injects the paste through it. In this way driving of the exudate into the surrounding tissues is avoided. He frequently fills only the bottom of the fistula to avoid intoxication.

Bismuth paste is extensively used for diagnostic purposes, being introduced into lengthy sinuses or fistulas, which are then traced with the X-ray.

The addition of iodine has been found to enhance the efficiency of bismuth paste in the treatment of **cancerous sinuses.** L. D. Green recommends: Bismuth subnitrate, 30 Gm. (1 ounce); petrolatum, 60 Gm. (2 ounces); white wax and paraffin, of each, 5 Gm. (80 grains), and iodine tincture, 2 Gm. (30 minims). The

iodine is added after the other ingredients are thoroughly mixed.

The *bismuth-iodoform-petrolatum paste* ("bipp"), rather extensively used during the World War as a dressing for **infected wounds**, is generally prepared according to the formula of Morison: Bismuth subnitrate, 1 part; iodoform, 2 parts; liquid petrolatum, enough to make a paste.

For dispensary patients the writers use a paste prepared according to the formula of Morison and an emulsion containing bismuth subcarbonate, 1 part; iodoform, 2, and liquid petrolatum, 4. In highly infected wounds they irrigate with sterile saline or 4 per cent. boric acid, swab thoroughly with 75 per cent. alcohol, shave and cleanse the skin with the alcohol, pack the wound and all sinuses and pockets tightly with the paste, and close it with silk or silk-worm gut sutures. Most of such wounds heal by first intention and leave insignificant scars. Tuberculous cervical adenitis with suppuration responds promptly to curettage followed by alcohol and the bismuth paste. Empyema cavities and lung abscesses also close promptly when filled with the emulsion and with the drainage tube in place. O'Connor and Kreutzmann (Jour. Amer. Med. Assoc., Dec. 15, 1917).

**Syphilis.**—Bismuth has proven a powerful weapon against this disease. While its value is not such as to displace mercury and the arsenicals, very many observers deem it of great value where other drugs are poorly borne, contraindicated or meet with resistance. Bismuth is regarded as having greater spirocheticidal power than mercury, though less than the arsenicals. It may be used alone or in conjunction with arsenic, mercury or both. According to Schwartz and Levin, bismuth destroys the spirochetes in the chancre, heals the latter

quickly, dispels the adenitis and affects the serum reactions favorably. It may abort syphilis, but is not as reliable as arsphenamin for this purpose. In secondary syphilis it acts and reduces the Wassermann more quickly than mercury, and there is less possibility of a Herxheimer reaction or neurorecurrence than after arsenic. It is also of value, though more slowly acting, in tertiary syphilis, neurosyphilis and congenital syphilis. In neurosyphilis the irritation as from arsenic is absent, and there may be decided subjective improvement without other changes. Bismuth has proved of special importance in cases with arsenical dermatitis, Wassermann-fast cases and obstinate or recurrent cases.

Bismuth intramuscularly acts more impressively on the symptoms than mercury, though it is less energetic than arsphenamin intravenously. It develops relatively few toxic properties as compared to arsphenamin and mercury. Seemingly, arsphenamin with bismuth acts more strongly than with mercury. The author substitutes bismuth alone for mercury where arsphenamin is badly borne or the condition of the veins interferes with arsphenamin injections. F. Juliusberg (Urol. and Cut. Rev., Jan., 1925).

L. T. DE M. SAJOUS,  
Philadelphia.

**BLASTOMYCOSIS.—DEFINITION.**—Blastomycosis is a chronic disease involving usually the skin, occasionally the lungs or other internal organs, caused by some form of blastomyces, a parasitic fungus.

Our knowledge of this disease began in 1894, when Gilchrist found that a supposed case of verrucose skin tuberculosis was in reality due to a yeast or mold fungus developing in the skin. Busse in the same year reported a case in which the lungs, lymphnodes, spleen, kidney, and bones were similarly involved, with a fatal

termination. Since that time increasingly numerous cases have been reported from Europe and in the United States, and according to Castellani and Chalmers, the disease is common in Southern India and Ceylon, the Philippine Islands, Indo-China, as well as, probably, in many other tropical regions. Within the United States, more cases have so far been reported from Chicago and its vicinity than from any other district.

**SYMPTOMS.**—The history and appearance of blastomycotic skin lesions suffice, in most instances, for a diagnosis. The lesion begins as a papule, which soon becomes a pustule. The surrounding skin then becomes inflamed and numerous abscesses of pin-head size are formed at its surface. The diseased patch becomes raised  $\frac{1}{4}$  to  $\frac{1}{2}$  inch above the surrounding skin and acquires steeply inclined margins. The contents of the small abscesses, which is glutinous and opaque, includes an abundance of the blastomycetes, which are seen also in sections of the involved skin. When the abscesses have emptied the skin exhibits a rough, uneven, "papillomatous" appearance, due to prolonged persistence of the solid partitions between the abscesses. When these break down, the appearance of the ulcer is less characteristic. Or, the abscesses may originally have been located at a greater depth in the skin, or subcutaneously, and the skin surface have become involved secondarily.

The history in cutaneous blastomycosis is typically initiated by an abrasion, cut, or other injury of the skin. After the latter has been involved exclusively for some time, perhaps for several years, the blastomycetes may enter the lymphatics or blood-stream and become disseminated in the general system. The lymphnodes become inflamed and form abscesses. Soon the lungs become involved—or, as is known to occur in a considerable percentage of cases, the lungs have been primarily affected, the original portal of entry having been the respiratory tract. The symptoms of lung involvement are cough, mucopurulent expectoration—sometimes blood-streaked—mucus, fever, night sweats, and marked prostration. The bones and joints may become affected. Usually the skin lesions run a

somewhat more rapid course after the lungs have become involved. The lung involvement generally presages a fatal ending. On the other hand, while the lesions are confined to the skin they are usually curable.

Case of blastomycosis of the skin in a patient aged 46 years. It had appeared 8 years before with lesions suggesting pustules, or boils, in the left axilla. After six months of futile therapy the entire lesion-bearing area was excised. After three years' respite the lesions appeared in the opposite armpit, and some months later in the groins, extending directly to the scrotum and anal furrow. There was at no time any ulceration, although the continuous secretion through minute sinuses was offensive. Gradually the general health became impaired. Persistent study of the secretion eventually led to obtaining a pure culture of yeast cells. Dörscher (Corresp. blatt f. schweizer Aerzte, Sept. 29, 1917).

The writer classifies the cases of blastomycosis he has seen into: (1) cutaneous type, (2) muco-cutaneous type, and (3) gluteal blastomycosis. The cutaneous type is characterized by verrucose patches with minute abscesses, and is quite common in Ceylon and other tropical countries. The muco-cutaneous type attacks not only the skin but also the oral mucosa and the pharynx, giving rise to numerous small papillomatous or frambesiform patches, which later may ulcerate. Gluteal blastomycosis presents a diffuse induration with numerous openings from which a thin purulent liquid exudes. Fungi of the genus *Saccharomyces* or *Monilia* are generally isolated from the pus. Castellani (Lancet, i, 847, 895, 1920).

#### ETIOLOGY AND PATHOLOGY.—

The vegetable organism causing the disease is a mold fungus which propagates by budding and is thus distinguished from the organism of "coccidial granuloma," which multiplies by endosporulation. The blastomycetes is a spherical body, unless observed during the process

of budding, when there may be seen a secondary node varying from a slight protrusion from the mother cell to a completely formed new cell ready to be cast off. No mycelium is seen in the tissues, but an abundant growth of it develops on culture media.

Among 47 American cases collected by Wade and Bell, the parts diseased, other than the skin, included the lungs, bones, spleen, kidneys, liver, lymph nodes, meninges, pleuræ, prostate, retropharynx, larynx, heart, peritoneum, pericardium, pancreas, adrenals, muscles, intestinal tract, epididymis and testicle, eye, tongue, tonsils, trachea, esophagus, and diaphragm. In lung involvement, there is little or no tendency toward cavity formation.

Report of cases unusual from the pathologic point of view. In 1 case there were extensive lesions of the spleen and liver, apparently due to the blastomyces, in which very few yeast cells could be found. In a second case there was an apparent secondary invasion by the blastomyces of a pellagrin suffering from pulmonary tuberculosis. In the skin lesion very interesting minute forms were found and specially studied. In a third case the heart was extensively involved, the condition being apparently unique. Widespread secondary bacterial invasion was noted in the liver, brain and bones. In a fourth case there was involvement of the lungs, liver, kidneys and lymph nodes, cutaneous and subcutaneous. In the fifth case the lungs, ribs, vertebrae and spinal cord were involved with the cutaneous and subcutaneous nodules present. Wade and Bell (*Arch. of Internal Med.*, July, 1916).

Report of a case of blastomycosis observed in Italy. The lesions, located in the mucosa of the mouth, pharynx, and larynx, were similar to those of the special Brazilian form of blastomycosis of the oral mucosa described by Lutz under the name of Brazilian zymonematosis. Treatment with iodine resulted in complete recovery. Brazilian cases usu-

ally end fatally. G. Basile (*Policlinico*, xxiv, sez. chir., 88, 1917).

**DIAGNOSIS.**—A positive diagnosis is based on demonstration of the blastomycetes in the pus from the skin or other lesions or in the sputum. The organisms are easily overlooked in stained preparations.

Coccidial granuloma, reported chiefly from California, is distinguished clinically from blastomycosis in being always systemic and nearly always fatal. It runs a more rapid course. The skin lesions fail to show the miliary abscesses of blastomycosis and in many instances appear to be secondary to the internal disease. Culturally, coccidial granuloma exhibits a circular, compact growth with sharp edges, while blastomycotic culture fades gradually into the surrounding medium.

Sporotrichosis, caused by a somewhat similar fungus, is distinguished clinically by primary involvement of the lymphatics, with secondary involvement of the skin and development of superficial abscesses along the course of the lymphatic vessels. The abscesses may be several inches apart and form a chain extending the entire length of an arm or leg.

Tuberculosis is clinically distinguished in that it most commonly affects the lungs, while blastomycosis most commonly affects the skin. Pulmonary blastomycosis runs a more acute course than lung tuberculosis, and sputum examination is diagnostic.

Of 29 collected cases, two-thirds occurred under the age of 34 years and all but 2 were in men. In at least 14 cases, the first symptoms were referable to the lungs, suggesting the respiratory tract as the usual route of infection. Pulmonary symptoms occurred sooner or later in all cases. **Vaccination** with a filtrate or suspension of triturated membranes of the organism, grown at room temperature in bouillon for 2 to 6 months, was practised in 2 systemic cases.

A von Pirquet test performed with the suspension was found of diagnostic value, a distinct papule, persisting 4 days, being produced. A.

M. Stober (Arch. of Internal Med., Apr., 1914).

The most important sign in interdigital blastomycosis is the *undermining of the advancing edge*. This feature is responsible for the failure of ointment to cure. The exciting agent must also be sought under the overhanging margin, where it is less contaminated by secondary organisms than toward the center. Berendsen (Arch. f. Derm. u. Syph., Mar., 1919).

Case in which a severe frostbite of the ears had seemingly been the starting-point, while in another instance, the initial infection had evidently been in the lung, the first evidence being a multiple arthritis. D. Y. Keith (Urol. and Cutan. Rev., Jan., 1922).

A man had bruised his finger while sorting soiled clothes collected from various hospitals. Four weeks later, a lesion appeared on the dorsum of the hand near the base of the finger, and subsequently similar lesions developed on the wrist. J. F. Langdon (Nebraska State Med. Jour., May, 1922).

The specific yeast fungus can easily be demonstrated by mixing a drop of pus with potassium hydroxide solution on a slide and examining unstained, microscopically. The fungi are seen as circular or oval budding bodies 15 to 30 microns in diameter (2 to 4 times the breadth of a red blood corpuscle) with a clear, doubly contoured membrane. B. F. Davis (Minn. Med., May, 1922).

In each of the writer's 3 cases the diagnosis wavered between syphilis, tuberculosis and mycosis until the discovery of blastomycetes. One out of the 3 patients, a case of 3 years' standing, died. The fungus was found in the lungs, spleen, kidneys and elsewhere. F. Terra (Brazil-méd., Jan. 27, 1923).

Case of blastomycosis with meningeal involvement. The patient was a deaf and dumb shoemaker aged 54 years. In the hospital a diagnosis of meningitis was made on admission. Lumbar puncture yielded a slightly cloudy fluid containing 19 leukocytes per cubic millimeter, 95 per cent. being lympho-

cytes. Many yeast-like cells staining with methylene-blue were seen; there were several hundred such cells per cubic millimeter. Some were smaller and others larger than a lymphocyte. They showed no ameboid movement. No tubercle bacilli could be found. The patient died, and the necropsy showed in the lungs, intestines and meninges structures resembling tubercles so closely that tuberculosis was diagnosed without a microscopic examination. Some time later, a guinea-pig, which had been given an intra-peritoneal injection of the patient's cerebrospinal fluid, was killed. Tubercle-like structures were found, and cultural and other investigations showed that the organism was probably the *Cryptococcus hominis* of Vuillemin. The meningitis must, therefore, have been blastomycotic, and the tuberculous-looking structures found in the lungs and intestines were probably of the same nature. The mode of infection was uncertain. There was no scarring of the skin, and it was deemed most probable that the germs entered by the respiratory tract, the patient's illness having begun with a cough. J. A. Voss (Norsk Mag. f. Laegevid., June, 1923).

Case of blastomycosis, with favorable issue, in a woman of 59 years. The primary site was in the vicinity of the left elbow-joint. There was chronic indolent ulceration of the skin and subcutaneous tissues, eventually involving the ulna, and associated with the discharge of mucoid pus, which contained the characteristic yeast-like bodies in large numbers. After involving the axillary glands by way of the lymph-channels, and showing very little tendency to involution after five months' surgical and caustic treatment (sharp spoon and pyrogallol locally), the disease entered on its secondary phase. Crops of new lesions began to make their appearance, evidently by way of the circulation, on the face, forehead and neck. They were all subcutaneous, and resembled erythematous, acneiform or scrofulodermatous eruptions. In contrast to the primary ulcer

on the forearm, these lesions were much more amenable to local treatment, and were soon healed after **scraping**. Some ulcerations in the mouth from which the organisms were recovered also involuted promptly. In about a year from the beginning of her symptoms the patient had completely recovered.

There were some unusual and important features in regard to the development of a specific immunity: (1) Antibodies could be demonstrated by complement-fixation tests in the serum in the primary stage, at a time when it was not possible to demonstrate cutaneous sensitization to autogenous cultures, and when there was but small tendency to healing and involution of the primary lesion on the forearm. These antibodies disappeared at a later stage. (2) The microscopic appearance of excised portions of the granuloma altered at successive biopsies, seemingly paralleling the development of the allergic sensitization. E. Ramel (Arch. f. Derm. u. Syph., cxlviii, 218, 1924).

Blastomycotic *interdigital erosion* is regarded by the author as a definite clinical entity, since during 2 years a yeast was found in all typical cases presenting themselves at his clinic. Buschke and others had already called attention to this superficial blastomycosis. The writer describes 2 additional cases. In one the lesions were situated on the inner aspect of the labia majora and labia minora. There were many small erosions alternately showing signs of healing and extending, thus closely resembling interdigital erosion in appearance. The patient had glycosuria; the association of diabetes and lesions containing yeast fungi has been previously noted. The second case showed a lesion on the hypothenar eminence and palm of the hand; it was manifest as an erosion 4 or 5 centimeters wide with an undermined, extending margin. A positive cultural test was obtained in both cases. J. Fabry (Derm. Woch., July, 1925).

Blastomycosis may be regarded as an *occupational disorder*, as shown by the

writer's clinical experience. It occurs in those working among animals or in those whose occupation brings them in contact with animal hides, refuse, etc. He reports 6 cases, one of which exhibited general systemic dissemination. Probably in most cases some excoriation is required for the entry of the fungus, although it may find its way into the skin *via* the hair-follicles. A possible means of inoculation lies in insect bites, particularly of the stable fly. No mycelium is to be found in the tissues, but solely spores with large sporangia. A. Ravogli (Acta Derm.-vener., Oct., 1925).

**TREATMENT.**—According to Stober, the influence of food, climate, and hygiene is important in the treatment. **Potassium iodide** in large doses seemed to cure one of Stober's 3 patients who recovered. For the *cough, pain* and *insomnia*, **codeine** is especially valuable. **Excision of skin lesions and aspiration and drainage of abscesses** give good results. Solutions of **copper sulphate** and **iodine** have proven useful for irrigation of abscesses. Treatment consisting of **potassium iodide** internally, and a **local antiseptic** and the **X-rays** externally, was found promptly curative by W. Frick in a case involving the nose and upper lip.

In a case of blastomycosis of 3 months' duration and involving both lids of the left eye, a **radium** varnish applicator, one-quarter strength, containing 0.04 Gm. ( $\frac{3}{4}$  grain) of radium barium salt, was applied for a total of 3 hours in fractional doses during the course of 3 weeks and caused the painless disappearance of the lesion. Two minute points appeared after a few weeks, but disappeared after 15 minutes' exposure. F. E. Simpson (Jour. Amer. Med. Assoc., Mar. 14, 1914).

Local treatment is rapidly successful if care is taken to reach the subcuticular advance under the peripheral overhanging margin. The writer uses dilute **iodine tincture** night and morning, with frequent applications of a 33 per cent. **salicylic** and **talcum** dusting powder. Berendsen (Arch. f. Derm. u. Syph., Mar., 1919).



The writer's patient was put on **potassium iodide**, 25 grains (1.7 Gm.) 3 times a day, quickly increased to 100 grains (6.6 Gm.), for 2 weeks. Dropping back to 180 grains (12 Gm.) a day, this dosage was kept up for 6 weeks longer. Locally, 1 per cent. **copper sulphate** solution was used, supplemented by the **X-rays**. The lesion healed in 3 months. Langdon (Nebr. State Med. Jour., May, 1922).

From South America have come reports of the value of **tartar emetic** given intravenously and by the mouth, with or without **heliotherapy**. According to Lozada (Anales de la Fac. de Med. de Lima, Peru, Nov.-Dec., 1920), the drug must be given in large doses by the vein up to the limit of tolerance, after beginning with small doses. He deems it necessary to continue the tartar emetic treatment for a year or more after healing of the lesions. The drug has a cumulative action.

**Fresh air, rest, and good food** are of prime importance. **Potassium iodide** by mouth in large doses has for years been used, with good results. **Arsphen-amin** intravenously has given marked benefit in some cases. In skin involvement, **excision** is indicated if mutilation is not thereby incurred. When excision is contraindicated, good results may usually be expected to follow the **X-rays** and **radium**. B. F. Davis (Minn. Med., May, 1922).

Six cases of exclusive **X-ray treatment** with satisfactory results. A second degree reaction was produced with unfiltered rays, using a gas tube with a 2-inch back-up at 6 inches (anode to lesion) focal distance. A **vaseline dressing** was applied throughout the period of reaction, lessening the pain and accelerating restoration of the skin to normal. J. N. McCoy (Urol. and Cutan. Rev., Jan., 1922).

In blastomycotic dermatitis tonics such as **iron** and **arsenic** gave better results than **potassium iodide**. The latter is, however, definitely required in cases with systemic dissemination. After the local lesion has been **scraped** and **cauterized** it should be dressed with gauze moist with **castor oil** and

**balsam of Peru**, equal parts. Local **X-ray** treatment is also of value. A. Ravogli (Acta Derm.-vener., Oct., 1925). S.

**BLEEDERS' DISEASE.** See HEMOPHILIA.

**BLEEDING.** See VENESECTION.

**BLEPHARITIS.—DEFINITION.**  
—Blepharitis is an inflammation of the lids. As the inflammation is usually confined to the lid margin, **marginal blepharitis** is more definitely descriptive of the condition.

It may exist alone, or it may be associated with acute or chronic conjunctivitis and lacrimal obstruction. In degree it may vary from a simple congestion or hyperemia to the ulcerative form with the formation of crusts and falling of the cilia or eyelashes.

Two varieties are usually recognized: (1) *Squamous* or *non-ulcerative*; (2) *ulcerative*.

**NON-ULCERATIVE BLEPHARITIS.—Symptoms.**—In this condition the lid margins may simply be hyperemic, with dry scales at the roots of the lashes. Because of its resemblance in appearance to seborrhea of the scalp, the disorder is sometimes spoken of as seborrhea of the lashes (*blepharitis ciliaris*). It is mild in type and not accompanied by the more serious complications observed in the ulcerative variety.

**Etiology.**—The most common cause of this form of blepharitis is uncorrected refractive errors and muscle imbalance. It is a part of the symptom-complex of accommodative and muscular asthenopia, ordinarily known as eye strain. In addition, it may follow exposure to irritants such as dust and smoke, loss of sleep, and exposure to bright lights.

In a modified form, it is associated with chronic gastrointestinal toxemia. In this variety, the lid margins are swollen and hyperemic, the skin of the lids is roughened, dry and scaly, and the tarsal conjunctiva is congested. Itching of the skin of the lids and of the conjunctiva is an annoying symptom.

**Prognosis.**—If the underlying causes of this form of blepharitis are corrected, recovery is prompt and complete. If the causes are uncorrected, it may develop into the more severe form of ulcerative blepharitis.

#### ULCERATIVE BLEPHARITIS.

—**Symptoms.**—This disorder is marked by swelling and thickening of the lid margins, chronic congestion, and the formation of yellowish crusts in which the cilia are matted together in spots and totally absent on other parts of the lid. The removal of these crusts is apt to carry the lashes with them, and ulcerated bleeding points are found underneath. As the hair follicles become infected, the cilia fall, and in the more chronic forms are not replaced by new cilia. If the cilia return, they often become misplaced, curve in against the cornea (*trichiasis*), and set up further irritation of the cornea and conjunctiva. As an extreme result, *entropion*, or turning in of the thickened lid margins, may occur.

**Etiology.**—The chief causes of this form of blepharitis are:—

1. Untreated or uncorrected non-ulcerative blepharitis.
2. Lacrimal obstruction, chronic nasal disease, chronic conjunctivitis.
3. Prolonged exposure to dust, smoke, and other irritants (occupational causes).
4. Systemic conditions which bring

about lowered resistance, such as phlyctenulosis, scrofula, inherited syphilis.

5. Exanthemata.

6. Chronic alcoholic intoxication.

7. Microörganismal infections.

**Complications.**—The complications and sequelæ which may follow the chronic ulcerative form of blepharitis are:—

1. Loss of the eye-lashes.
2. Trichiasis (turning in of misplaced lashes).
3. Entropion (inturning of the lids).
4. Ectropion (eversion of the lids).
5. Chronic conjunctivitis.
6. Lacrimal obstruction.

While chronic conjunctivitis and lacrimal obstruction may be an etiological factor in the production of ulcerative blepharitis, eversion of the puncta, when the lids become thickened from chronic blepharitis, may in turn become the cause of lacrimal obstruction and chronic conjunctivitis because the tears and secretions cannot be carried away through the natural channels.

*Blepharadenitis* is only an aggravated sub-acute or chronic form of blepharitis ciliaris, in which the mouths of the Meibomian follicles have become closed and the lining membrane of the glands has become sub-acute or chronically inflamed. Retention cysts and abscesses with pyogenic membranes secrete pus from granulating sacs and deform the lid.

Unless every particle of **diseased gland** with its pyogenic membrane be carefully **removed**, recurrence will take place, and careless removal (enucleation) means injury to the tarsal cartilages, with resulting deformity, "wrinkled lid," and destruction of the cornea from irritation and deposit of connective-tissue macules or pannus.

*Scabies of the palpebral fissure* is not a commonly recognized condition. Raehlmann, however, has described this form of scabies. The acarus seems to affect the ciliary follicles and may thus escape detec-

tion. There is considerable blepharitis, accompanied by itching and tingling, along the free border of the eyelids. The lashes fall out. There is hyperemia of the inner marginal zone and of the neighboring skin. A honey-like secretion covers the border of the eyelids and adheres especially to the point of emergence of the lashes. There is often a considerable degree of conjunctivitis. The treatment recommended consists in applying an ointment of **balsam of Peru**, 2 parts; **lanolin**, 6 parts; or, **balsam of Peru**, 2 parts; **lanolin**, 4 parts; **oil of sweet almonds**, 2 parts. This must be applied every day, and left on for about half an hour. The condition may be cured in four or five days, but the applications should be continued for some time.—Ed.

**TREATMENT.**—In either form of the disease, the first step in the treatment is the correction of the underlying factor. All refractive and muscular disturbance should be carefully corrected by the prescribing of suitable glasses and proper muscle training. Constitutional disorders should be met by the proper therapeutic and hygienic measures.

In the cases in which the alopecia of blepharitis marginalis is present without ulceration or apparent desquamating conditions, or such as may be due to parasitic or microphytic causes, in persons who have neither syphilis nor leprosy, the application of **phenol**, according to Reynolds, often produces brilliant results. He has never seen hair restored in palpebral alopecia in a subject of general alopecia. In syphilitic subjects, where the hair has fallen from the brow, eyelids, and head, all efforts at restoring it to the lids by local applications have failed, nor has he seen the lashes reappear in syphilitic cases under constitutional treatment.—Ed.

During and after the exanthemata and eruptive diseases of childhood, the eyes should receive careful attention and soothing collyria should be prescribed.

For this purpose, a most satisfactory eye-wash is the following:

℞ *Acidi borici* ..... gr. x (0.6 Gm.).  
*Sodii boratis* ..... gr. v (0.3 Gm.).  
*Aquæ camphoræ* .. f3j (4 c.c.).  
*Aquæ rosæ*,  
*Aquæ destillatæ*,  
 āā q.s. ad ..... f3j (30 c.c.).—M.

Ferro has reported excellent results from the following ointment:—

℞ *Copper sulphate*,  
*Ichthylol* ..... of each gr. viij (0.5 Gm.).  
*White vaselin* ..... 3j (30 Gm.).

It does not affect the cornea or the conjunctiva, and the effects were very uniform. It is useful in all forms of the affection. The ichthylol acts as an antiseptic and stimulant, while the copper sulphate exerts astringent properties, reducing the congested sebaceous glands.

Pick has obtained good effects in the treatment of blepharitis ciliaris by the application of the following ointments:—

#### I.

℞ *Salicylic acid* ..... gr. ivss (0.3 Gm.).  
*Zinc oxide* ..... gr. xv (1 Gm.).  
*Wool fat*,  
*Petrolatum*,  
 of each ..... gr. lxxv (5 Gm.).

M. et ft. ungt.

Sig.: For external use.

#### II.

℞ *Tumenol* ..... gr. ivss (0.3 Gm.).  
*Zinc oxide* ..... gr. xv (1 Gm.).  
*Petrolatum*,  
*Wool fat*,  
 of each ..... gr. lxxv (5 Gm.).

M. et ft. ungt.

Sig.: For external use.

The two ointments are applied at night, every second day. If suppuration ensues, the lashes should be plucked out and the parts cauterized with **silver nitrate**.—Ed.

In the non-ulcerative form these measures suffice to relieve the condition. In the ulcerative variety, they must be supplemented by more active local treatment. All **crusts** should be gently **removed** by warm **solutions** of **sodium bicarbonate**. Care should be observed in order not to injure the epithelium, which would cause

bleeding. The ulcerated areas may be touched gently with a solution of 1 or 2 grains (0.06 to 0.13 Gm.) of **silver nitrate** to the ounce (30 c.c.) of water. Loose cilia should be removed.

A good **cleansing** given by the surgeon himself, and a final light swabbing with a weak solution of **silver nitrate**, is deemed of particular efficacy by Harman. Then the application of a smooth antiseptic ointment will keep the lids soft and reduce the liability to the collection of more crusts and scabs. Plain **boric ointment** in yellow vaselin, or a doubly diluted ointment of **ammoniated mercury**, or the **yellow oxide of mercury** in a mixture of lanolin and vaselin to the strength of 1 per cent., are all of value. These measures will do much to reduce the unsightly ravages made by the disease. To get at the real cause, however, the refraction of the eye must be made out, and any irregularity found must be corrected with glasses.—Ed.

Use of a hypertonic solution, such as simple **syrup**, advocated to produce a strong osmotic current on the surface of the infected mucosa, with the purpose of washing out bacteria or particles of matter deeply embedded in glands or interstices, where antiseptics cannot reach. In a case of blepharitis of 8 years' standing which had resisted all other treatment, a drop of syrup was instilled every night. The resulting marked burning sensation was followed by secretion which washed out small glandular concretions. Early improvement was noticed and at the end of 3 weeks the congestive symptoms had disappeared. E. Doumer (Bull. de l'Acad. de méd., Feb. 27, 1923).

The following ointment is of much value in removing the crusts and in healing the ulcerated lid margins:—

℞ *Phenolis* ..... gr. j (0.06 Gm.).  
*Ichthyolis* ..... gr. iv (0.26 Gm.).  
*Petrolati* ..... ʒj (30 Gm.).

M. ft. ung.

Sig.: The lid margins may be gently massaged with this ointment three times daily.

After the crusts are removed, **yellow oxide salve** (yellow oxide of mercury,  $\frac{1}{4}$  to  $\frac{1}{2}$  per cent. in petrolatum) is soothing and efficacious.

May advises ichthyol in various combinations:—

℞ *Ichthyolis* ..... gr. vj (0.4 Gm.).  
*Petrolati* ..... ʒij (8 Gm.).

M. et ft. ung.

Sig.: Apply to lid margins after cleansing.

℞ *Ichthyolis* ..... gr. x (0.65 Gm.).  
*Ung. zinci oxidi* ... ʒij (8 Gm.).

M. et ft. ung.

Sig.: Apply to lids after removal of crusts.—Ed.

If lacrimal stenosis is present, the **puncta** should be **opened** and the **lacrimal sac** should be **washed** by warm sterile water or by sterile normal saline. In fact, in the ulcerative form of blepharitis, even though there may be no actual stenosis of the lacrimal system, recovery is hastened by frequent lavage of the lacrimal sac.

Turnbull found the following prescription for cases of narrowing of the tear-ducts an especial favorite with young people, often anxious suddenly to do away with red eyelids. It can be used with impunity, but must never be replenished without another prescription. The cocaine may, for evident reasons, be omitted, but is of value, prolonging the effect of the adrenalin:—

℞ *Boric acid powder* .. gr. x (0.65 Gm.).  
*Cocaine hydrochloride*  
 (2% solution) .... fʒj (4 c.c.).  
*Adrenalin hydro-*  
*chloride* (1:1000  
 solution),  
*Water* ..... of each fʒij (8 c.c.).

Sig.: Put one drop into either eye before and after each meal, or oftener.

In *furunculosis* of the lids and *styes* treatment by **vaccines** is deemed useful by the writers. The staphylococcus is regarded as the usual cause; it may be combined with the pneumococcus and streptococcus, the latter, indeed, often predominating in the pus from furuncles along the lid margin. The

lesion always begins with hair bulb inflammation (folliculitis). There is a marked tendency to recurrence. Results clinically obtained with vaccines showed that they are effective when properly adapted to the existing condition. Autogenous vaccines are preferable to the stock variety in the treatment of styes. De Lapersonne and Casteran (*Arch. d'ophth.*, Nov., 1922).

LUTHER C. PETER,  
Philadelphia.

**BLOOD-PRESSURE.**—By blood-pressure is meant the arterial tension or pressure of the blood in the vessels within which it is contained.

The best information as to existing circulatory conditions is obtained by determining the blood-pressure in the morning before rising from bed. A pressure nearly normal at this time points to any high pressure at other times as being probably of the functional type. L. Roemheld (*Münch. med. Woch.*, Aug. 3, 1923).

**SYSTOLIC AND DIASTOLIC PRESSURE.**—Blood-pressure is divided into the maximum or systolic pressure and the minimum or diastolic. The systolic is the greatest pressure exerted, and takes place during systole of the heart; the diastolic is the lowest pressure, and occurs in the cardiac cycle just at the beginning of systole, or at the end of diastole, the time when most of the blood has passed through the capillaries into the veins.

**PULSE-PRESSURE.**—From these we obtain the pulse-pressure, which is the difference between the diastolic and the systolic, and also the mean pressure, which is about the average between the systolic and the diastolic readings, but has little clinical value and is seldom used.

**IMPORTANCE AND APPLICATIONS OF THE BLOOD-PRESSURE.**—What is the application and

meaning of blood-pressure determinations in special conditions, and how reliable are they when other means fail us?

In clinical blood-pressure determinations it should be remembered that the pressure, normal or abnormal, is never constant, varying with exercise, digestion, disease, and with the nervous and mental state. Often the systolic pressure when first taken may be, through a psychic effect, 10 or 15 points higher than it will be if the air is allowed to escape from the cuff and the estimation repeated. Further, there are many people who may be said to be by nature low-pressure or normally high-pressure patients. Not infrequently a man of 50 will be in perfect health with a pressure of 125 or 135 systolic, while another, also in perfect health, will range from 145 to 155. Variations of only 5 to 10 points above 100 in diastolic pressures have significance.

It is possible by studying diastolic and systolic pressures to reach a fairly definite conclusion represented by figures as to what has been called by Barach the "energy index" of the circulation. To do this, the diastolic and systolic pressures are added together and multiplied by the pulse rate; thus, if the diastolic pressure is 70 and the systolic pressure is 120, making a total of 190, and this figure is multiplied by a pulse rate of 72, the energy index will be 13,680, and this figure, according to Grover, represents a normal energy index, although the range in perfect health may vary from 13,000 to 20,000. It is claimed that when the figure exceeds 20,000 an excessive circulatory load exists. Editorial (*Ther. Gaz.*, Feb., 1926).

The investigations of Briggs and Cook clearly showed blood-pressure determinations to be one of the most important aids in diagnosis and treatment of eclampsia and cardiorenal disease, and its undoubted value in typhoid fever medication in children;

in surgery before, during, and after operative procedures, and injuries of the head, etc.

In life-insurance examination almost all companies now recognize blood-pressure estimation as a necessary procedure. The reason for this is very clearly shown in the statistics from the Northwestern Life Insurance Company, which was one of the pioneers in taking blood-pressure readings on its applicants. In a letter to their examiners they say: "The statistics on 1247 cases at all ages, in which there was a blood-pressure of 150 mm. mercury and over, show a mortality two and one-half times greater than the general average mortality of the company covering the same period. In 891 of these cases there was no other impairment recorded in the application when received at the home office. All these risks would have been granted insurance had not blood-pressure been taken. A careful study of the statistics of this company demonstrates, without a doubt, that the use of the sphygmomanometer is indispensable in our examination for life insurance. The statistics also demonstrate, in our opinion, that the use of the sphygmomanometer will be of equal value to the practitioner in his general practice, and that no physician should be without this valuable aid in diagnosis."

Blood-pressure determinations are of value also to specialists in eye and ear conditions; in fact, there is no branch of medicine in which blood-pressure is not significant, and often an aid when other means of diagnosis have not been sufficient.

**HISTORICAL.**—Going a little into the history of blood-pressure

determinations we find it dates back to 1828, when Poiseuille introduced the first U-tube mercurial manometer.

Shortly afterward Ludwig devised the kymographion, a manometer connected directly to an open artery, and recording on a revolving cylinder; but it was not until 1876 that a useful apparatus for estimating blood-pressure in man was used by Marey, by which he could determine both systolic and diastolic blood-pressure.

There was, however, no general use of blood-pressure apparatus until some eleven years later (1887), when v. Bosch brought forward his apparatus, consisting of a small rubber bulb filled with water connected with a mercurial manometer; the bulb being pressed upon the radial artery until the pulse was just obliterated, and the pressure read off the manometer. V. Bosch later modified his apparatus by using an anaëroid in place of the mercurial manometer.

V. Potain further substituted on the v. Bosch apparatus air in place of water, which was a great advance, but both instruments have a large possible error<sup>2</sup> which Tigerstedt claims has reached 78 mm.

All our modern apparatus dates from 1896, when Riva-Rocci, in Italy, used a rubber bag, 5 cm. wide, surrounded by an inelastic material, and completely encircling the arm. This cuff was connected, by rubber tubing, with a reservoir of mercury having an upright capillary tube, alongside of which was a mm. scale. Air was pumped into the cuff, compressing the brachial artery until the pulse below the band was obliterated, and then, by releasing the air slowly, he determined when the pulse reappeared, and thus obtained a reading

of the maximum or systolic pressure, shown by the column of mercury in the capillary tube.

All instruments which give accurate readings have utilized the principle of the pneumatic constricting band, except that now the width of the cuff is at least 12 cm., as the narrow cuffs, such as the original Riva-Rocci, give too high readings. This very important error was shown by the work of v. Recklinghausen to be due to the loss of pressure in compressing the tissues, and that it could be eliminated if a cuff from 12 to 15 cm. wide were utilized. Theo. C. Jane-way stated that he had found in high-tension cases a 5-cm. cuff to register as much as 60 mm. higher than a 12-cm. cuff.

All our modern blood-pressure determinations, as on the Riva-Rocci instrument, are recorded as the pressure measured by the height of a column of mercury of so many mm., or, in other words, mercury is the standard on which blood-pressure readings depend.

**METHODS OF MEASURING BLOOD-PRESSURE.**—As all accurate modern instruments for estimating blood-pressure utilize the pneumatic principle of the Riva-Rocci, the methods of blood-pressure determinations are about the same, as follows: The apparatus used being set up ready to operate, the pneumatic cuff is adjusted snugly, and without compression, to either the thigh or the arm, usually the arm, taking care that the cuff is at the level of the heart. The cuff is then inflated until the pulse below the constriction is obliterated, which is determined by palpating the artery. The estimation of blood-pressure is

then made by either one of two methods: 1. The old, or palpation, method. 2. The new, or auscultation, method, described in 1906 by Korotkoff.

**PALPATION METHOD.**—(a) **Systolic.**—After obliterating the arterial pulsation in the vessel below the cuff, slowly release the air-pressure, allowing the mercury to fall evenly, and note the height of the column when the pulsation reappears to the palpating finger. This gives the systolic or maximum pressure, and will be found easy to obtain on all instruments.

The most satisfactory and probably the most trustworthy determination of the systolic pressure is by the palpatory method, while for the diastolic pressure either the change of sound or the disappearance of all sound should be taken as the criterion, depending upon the accuracy of the determination in each individual case. The point selected should be recorded and always used in the future work with the same case. The systolic pressure is unquestionably of much more value than the diastolic and, contrary to general opinions, the relative range of variation in the normal subject is wider in the diastolic than the systolic. The pulse pressure is subject to still greater variations, and several factors beside the volume of blood ejected from the heart influence it, *e.g.*, vasoconstriction and dilatation, either generalized or local. The systolic pressure is certainly of value in arterial and renal diseases, cerebral pressure, the toxemias of pregnancy, Addison's disease, and to a less extent in the diagnosis of aortic insufficiency.

A very valuable use is in the early discovery of *pulsus alternans*, which can often be brought out by careful adjustment of the cuff pressure so as to cut out every alternate feeble beat, even where the alteration is not otherwise appreciable by

the finger. E. S. Kilgore (Lancet, Aug. 24, 1918).

(b) **Diastolic.**—1. After taking the systolic pressure allow the mercury to fall slowly, and note the varying degrees of oscillation of the mercury column. Read the scale at the base of the maximum fluctuation and it gives the diastolic pressure. 2. Or, when the first change from a small to a full, bounding pulse is noted, read the height of the mercury column, which gives the diastolic pressure.

Considerable stress is laid upon the determination of the diastolic pressure. L. F. Mackenzie refers to it, in fact, as the fundamental pressure. It is much less influenced by emotions than the systolic; measuring, as it does, the peripheral resistance, it is the pressure which the heart must first overcome, and which imposes constant strain upon the aorta and aortic valves. As stated by Warfield, the diastolic pressure is more constant for any individual than the systolic. It is probably a more accurate index of high or low tension than the systolic pressure because, as stated, it measures the amount of peripheral resistance. The *pulse-pressure* represents the actual head of pressure which is forcing the blood to the periphery—the efficiency of the heart action in the face of the existing state of peripheral resistance. A falling pulse-pressure gives the earliest indication that a patient is not doing well, while a rising pulse-pressure points to favorable progress.

The formula of the normal relation of the systolic, the diastolic, and the pulse-pressure is 3:2:1; for example, systolic 124, diastolic 82, pulse-pressure 42. Faught (Med. Record, Mar. 10, 1917).

In the prognosis of high blood-pressure, the diastolic pressure is more instructive than the systolic. Its normal range is 70 to 90 mm. Hg. Of 34 persons with diastolic pressures above 135 mm., seen before 1919, 26 were known to have died. With a permanently high diastolic pressure, refractory to treatment, a survival of not more than 5 or 6 years can be anticipated. Lian,

Broca and Clément (Presse méd., Sept. 17, 1921).

At low diastolic pressures a very considerable output is attained for quite a small pulse pressure, while at high diastolic pressures the output remains small for very high pulse-pressure. It is thus impossible for a person with a high diastolic pressure to attain a considerable output without developing a dangerously high pulse-pressure and throwing an enormous strain on the heart. J. C. Bramwell, A. C. Downing and A. V. Hill (Heart, Oct. 30, 1923).

**AUSCULTATION METHOD.**—(a) **Systolic.**—As in the palpation method, having inflated the cuff until the pulse is obliterated, place the bell of an ordinary binaural stethoscope over the artery just below the cuff. Now release the air-pressure slowly, and listen with the stethoscope. When the first cardiac beat passes the constricting cuff a loud, clear thump is heard, and the true systolic pressure is obtained by reading the height of the mercury column.

(b) **Diastolic.**—In taking the diastolic continue to release the air-pressure and listen over the artery. The thumping sound is followed by a murmur, and then by a second thumping sound which becomes fainter and suddenly disappears. The diastolic pressure is usually read when the second thumping sound passes into the final dull tone (4th phase). Some, however, have made the reading at the moment of disappearance of all sound.

This last auscultation method has almost revolutionized the determination of blood-pressure, for diastolic pressure can be as easily and accurately determined as systolic pressure, a result previously impossible of attainment, there being such a large personal element in obtaining the diastolic pres-



sure that most observers did not attempt it.

The diastolic and pulse-pressure (difference between systolic and diastolic) are thus accurately determined by this method, and are often of even greater importance than the systolic.

Experiments on dogs showed that whereas the pulse-pressure in the larger arteries (femoral) varies extensively, it varies within narrow limits only in the small ones (dorsal artery of the foot). These results supply an experimental explanation for the fact that in man uniform pressure readings were obtained by Gaertner's method at the digital artery. Cohn and Lundsgaard (Jour. Exper. Med., Apr., 1918).

Here I wish to make clear a point which has created considerable confusion in the past, the relation of the inertia of the mercury column to the determination of the diastolic pressure, and also as to whether it is of importance for the column of mercury to fluctuate with each pulsation of the heart. Were we to adhere to the old method of reading the diastolic pressure the mercurial inertia might be of slight importance, but from a practical standpoint of little significance.

When we employ the auscultation method for determining diastolic readings, a method now almost universally used on account of its ease and accuracy, the lack of fluctuation of the mercury has absolutely no disadvantage. On the contrary, it becomes easier to obtain the true pressure reading where the column is not actively oscillating, as is the needle of an aneroid. Blood-pressure determination is a question of the pressure existent in the arterial system, not of the pulsation of the heart.

Diastolic pressure depends largely upon systolic, but increases propor-

tionally more slowly. In the diastolic pressure a total range of 30 mm. Hg must be allowed, on account of the effects of meals, emotions and similar factors. Diastolic pressure may show a relative increase upon a fall of the systolic. This may indicate myocardial weakness. Diastolic hypertension is important in connection with sensory heart conditions, as in Graves's disease and nephritis. Diastolic hypotension attends aortic insufficiency, arteriovenous aneurism and patent foramen ovale. J. T. Peters (Nederl. Tijds. v. Gen., Oct. 18, 1924).

In the **auscultation method** it is largely a question of the physics of fluids, *viz.*, the artery is constricted by means of the pneumatic cuff; below it there is no arterial flow, and the vessel walls are in a semirelaxed condition. The blood-pressure is lowered in the cuff gradually until the heart has power enough to drive some blood into the relaxed vessel beyond. The sudden flow of blood into the relaxed vessel sends the wall into vibration, and a loud, clear thump is heard which gives the systolic pressure. In making the diastolic estimation there is again a physical condition of a fully expanded artery above the pneumatic cuff, a constriction under the cuff, and an enlargement below. Fluid passing from a large tube through a constriction into a large opening is known to produce a murmur; on the other hand, when the caliber of the tube is uniform, or, in other words, when the diastolic pressure is able to overcome the constriction of the cuff, there will no longer be any sound. It can easily be seen that it makes no difference whether the mercury column records each pulsation of the heart or not, but that it shows much more easily and accurately the correct blood-pressure than

could be read if it were fluctuating very actively.

The beginning of regular, rhythmic snapping sounds is the best criterion point for use in measuring the systolic pressure. The criterion for measuring the diastolic pressure is the lowest point where the snapping sounds are heard, or where they just cease. Brooks and Bleile (*Jour. Amer. Med. Assoc.*, Aug. 17, 1918).

C. F. Judson and Percival Nicholson made 2300 blood-pressure observations upon **children** whose ages ranged from 1 to 14 years. They found the auscultatory method superior to the palpation method. The gradual increase in the blood-pressure takes place up to 13 years of age. From 10 to 14 years, at puberty, there is a rapid increase in the pressure, owing to the great increase in the size of the heart at that time. The variation from 4 years up to puberty is less than 8 mm., and the total rise from 4 to 14 years of age is 14 mm.

Examining 102 normal **newborn infants**, the writers found that the blood-pressure on the first day after birth averaged 43 mm. Hg. Up to the third day it rose comparatively rapidly. From then on it increased more slowly, but steadily, until the end of the first month. At the end of the first week it was 60; at the second, 70, and at the end of the first month, 82. Seitz and Becker (*Zentralbl. f. Gynäk.*, Nov. 20, 1920).

Having taken blood-pressure readings in 102 men ranging in age from **75 to 90 years**, the writers note that up to middle age the heart, as the chief factor concerned in blood-pressure, may generally be considered a constant factor, while in later life it cannot, since post mortem examinations in old men have shown the majority to have deteriorated cardiovascular systems. Most of their 102 men had systolic pressures of 130 to 169 mm. Hg, and diastolic pressures of 70 to 89. On

the other hand, other men with no signs of either hypertension or hypotension had readings varying from 190 systolic and 100 diastolic to 95 systolic and 45 diastolic. It must be presumed, on the basis of these findings, that an adaptation compatible with extended life can be arrived at between the weakened heart and the metabolism of old age. Thompson and Todd (*Lancet*, Sept. 2, 1922).

According to 14,934 blood-pressure tests in university students, the pressure does not uniformly increase with age. In men the average pressure actually declines from the ages of 17 to 21 years in males and from 17 to 25 in females. Thereafter, it remains about the same in men until after 50 years, whereas in women it rises rapidly after 25 years and very rapidly after 40. W. C. Alvarez (*Arch. of Int. Med.*, July, 1923).

The normal limits of systolic pressure after the 20th year range between the sum of 90 plus  $\frac{1}{2}$  the age to 130 plus  $\frac{1}{2}$  the age (auscultatory method). At 60 years in men, however, there occurs an abrupt rise from 140 to 145 mm., then a gradual increase to 150 mm. at 70 years. In women, the author finds, the pressure dips somewhat between the ages of 30 and 50. J. T. Peters (*Nederl. Tijd. v. Geneesk.*, Nov. 3, 1923).

The blood-pressure of 1000 healthy soldiers (age, 20 to 25 years; pulse, not under 60 nor over 90; ave. height, 174 cm.; ave. weight, 143 lbs. Danish) ranged from 90 to 170 mm. Hg, with an average of 119 mm., by the Riva-Rocci method. A. Faber (*Acta med. scandinav.*, Oct. 15, 1924).

Determining the blood-pressure in **627 children**, the writer found the average systolic pressure in boys between 7 and 11 years to be 98 mm. Hg, and the diastolic, 61 mm. In girls of the same age, the figures were 93 and 58. In boys between 11 and 14 years, the systolic averaged 107, the diastolic, 71; in girls, the figures were 106 and 63. Thomas (*Schweiz. med. Woch.*, Sept. 24, 1925).

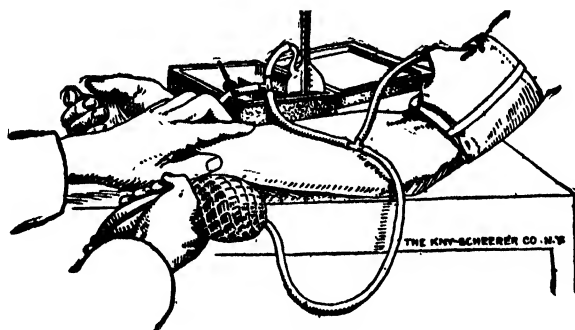
**CHOICE OF AN INSTRUMENT.—**

The number of instruments at present available for blood-pressure work is legion, and it is decidedly confusing, to one entering this field, to select a good practical instrument.

Among the recognized desiderata in a practical sphygmomanometer are, that it shall give permanently exact readings; that the cuff must have a width of at least 12 cm.; that the tubing used must be practically non-distensible; that its application must be simple and require little time, and that it be at once compact, light, substantial, and not too costly.

when applied over the brachial can be filled with air until the pulse at the wrist is just obliterated. This is a fairly accurate instrument for determining systolic readings, but, not having a good air release, is not practical in determining diastolic pressures. It is inaccurate in that it uses a 5-cm. cuff, which gives too high readings. Though by the use of a jointed tube it is fairly compact, the mercury is easily spilled and the instrument fragile. Its double bulb for inflation is also a constant source of annoyance from blowouts.

Now turning to cut No. 2 the



1. Cook's sphygmomanometer.

**Instruments.**—As it is impossible to describe all the forms of apparatus, a few of the simpler and more practical instruments may be mentioned. The desirable features in such instruments will best be understood by beginning with the older types.

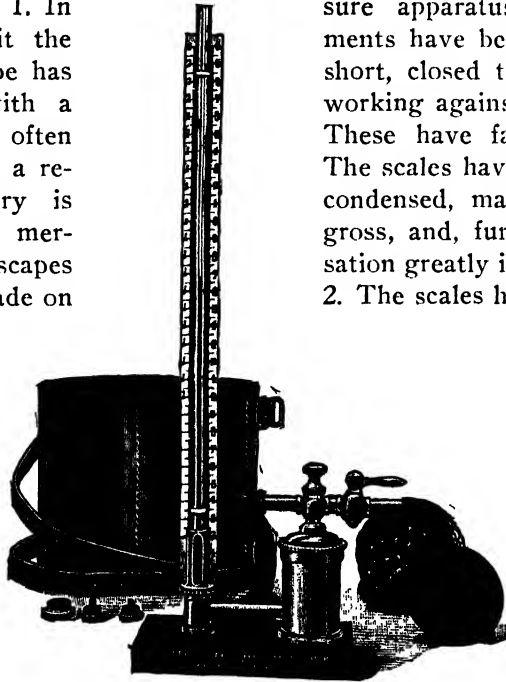
The simplest mercurial instrument is the Cook modification of the Riva-Rocci. (See cut No. 1.) It utilizes all the principles of the original Riva-Rocci instrument, consisting of a constricting pneumatic cuff connected with a mercurial manometer, and having a means of inflation. The cuff

original Stanton apparatus is seen—a reliable instrument, but no longer manufactured. It was a large, heavy instrument having several defects, as: 1. The use of a 10-cm. cuff, which gave too high readings. 2. It was not very portable, requiring to be taken apart and set up when used in general practice. 3. It was difficult to prevent the mercury from escaping. 4. It had the same defect as the Cook apparatus in that it used a double rubber bulb for inflation. However, it was largely adopted and gave accurate readings with a wide cuff.

Cut No. 3 shows the Janeway apparatus, a more portable instrument devised by Theo. C. Janeway. This instrument has the advantage over the others named above, in that it used an accurate 12-cm. cuff, and hence the readings were correct on most of the instruments. But it also has its defects: 1. In order to carry it the end of the U-tube has to be closed with a cork, which is often forgotten and, as a result, the mercury is spilled. 2. The mercury often escapes from the joint made on

found to vary 40 mm. 5. The rubber tubing comes in direct contact with the mercury, and sulphide of mercury is formed, coating the glass black and causing friction, with inaccurate readings.

In order to attain portability, a greatly desired feature in blood-pressure apparatus, several instruments have been made having a short, closed tube with mercury working against the inclosed air. These have failed because: 1. The scales have necessarily to be condensed, making the readings gross, and, further, this condensation greatly increases any error. 2. The scales have to be specially



2. Stanton's sphygmomanometer.

the long arm of the U-tube. 3. As made now, there is a wide metal union which obstructs the reading for some 30 mm. in the middle of the scale. 4. Like all U-tube instruments, it utilizes a scale condensed one-half to allow for the descent of one column while the other rises. This might be accurate were it not impossible to obtain glass tubing of uniform caliber; consequently, there is often an inaccuracy, one column being balanced against the other, and therefore any error is multiplied by two. Two instruments recently examined were

standardized by comparison with a mercurial column, and, being fixed on the glass, cannot be adjusted to allow for any change in the compressibility of the inclosed air column, which varies greatly according to moisture, temperature, and climate.

The author's instrument (cut No. 4) is simply a short form of mercurial instrument, utilizing the open tube, and so arranged that the mercury needs no pouring and cannot be spilled. By the use of a steel stopcock and flint glass there is no corrosion of the mercury. The instrument

is only  $13\frac{1}{2}$  inches long, and when closed will fit in the ordinary doctor's bag. Accuracy is maintained by the use of a scale adjustable to the mercury level, allowing for changes of climate and temperature, and by the use of a wide, easily adjusted, soft cuff (14 cm.) (cut shows old type of rigid cuff). The air-pressure is easily and steadily released by means of a needle-valve.

Among the other mercury instruments, similar in their essential principles, may be mentioned the B-D, Faught, and Baumanometer.



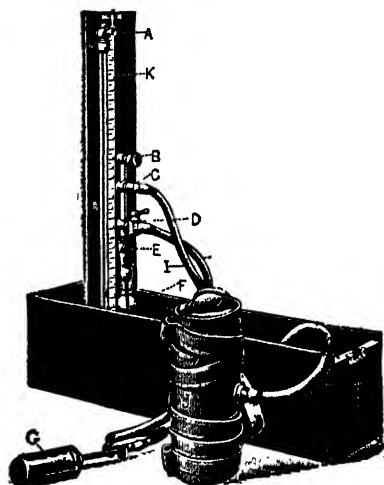
3. Janeway's sphygmomanometer.

There are several forms of especially accurate instruments, but owing to their expense and size they are not available in general practice, *e.g.*, the Erlanger, etc.

In addition, there are the aneroid instruments, operating on the general principle of the aneroid barometer. These instruments, while convenient, have been reproached with requiring frequent standardization by comparison with a mercurial manometer, if continued accurate results are to be obtained, as well as with being difficult to repair.

The ordinary form of aneroid sphygmomanometer, and its mode of employment

in the auscultatory method, are illustrated in cut No. 5. In this type of instrument the atmospheric pressure constitutes the constant pressure within the aneroid chambers (instead of a vacuum, as in aneroid barometers), and the surrounding variable pressure is that existing in the closed pneumatic system which includes the cuff about the patient's arm, which is therefore variable according to the inflation practised by the observer. The pressure existing at any given moment in the cuff is shown by the position of the pointer on the dial, upon which are seen figures representing millimeters of mercury. The arm-band and air-



4. Nicholson's sphygmomanometer.

pumping device are essentially the same as in the mercury instruments, and, similarly, either the auscultatory or the palpatory method may be used, preference being given to the former where the diastolic pressure is desired. There is also the possibility, more especially with the aneroid instruments having large dials, of applying the *oscillatory method* of determining the diastolic pressure. In this procedure, after the systolic pressure has been taken, the pressure in the cuff is allowed to descend a few millimeters at a time, the size of the oscillations described by the hand over the dial being meanwhile continuously and carefully watched. A point will be noticed at which, after the greatest oscillations have taken place, the size of the oscillations suddenly diminishes. At this point the lowest

reading of the excursion of the hand over the dial constitutes the diastolic pressure reading.

Among the best known of the aneroid sphygmomanometers are the Tycos, Faught aneroid, Sanborn and Boullite. Some instruments embody a self-verifying feature whereby, if the hand over the dial when not in use falls within a certain restricted length of the scale, the instrument may be assumed to be in working order and capable of giving sufficiently accurate readings. An additional device which makes for convenience is a special stethoscope with adjustable bracelet which secures the bell of the stethoscope over the artery and makes it unnecessary for the observer to hold it in place. A further refinement which dispenses with both auscultation and palpation is the use of a second manometer fastened about the forearm, which shows when the pulse wave begins to come through.

With the French instrument known as the Pachon oscillometer, auscultation and palpation are likewise both dispensed with, and both the systolic and diastolic readings are based solely on observation of the oscillations of the hand over the dial. With this instrument the readings are apt to be higher than with mercurial sphygmomanometers, especially in the higher ranges of the systolic pressure.

**THE BASIS OF BLOOD-PRESSURE.**—Blood-pressure depends on four main factors: 1. Cardiac strength. 2. Peripheral resistance in the vessels. 3. The elasticity of the vessel walls. 4. The volume of blood.

During cardiac systole the pressure in the aorta reaches a maximum, and shortly after the aortic valves close. The pressure from then on until the next systole is maintained by the elasticity of the vascular walls, and as the blood is being forced on through the capillaries the pressure gradually falls and reaches its minimum at the end of diastole.

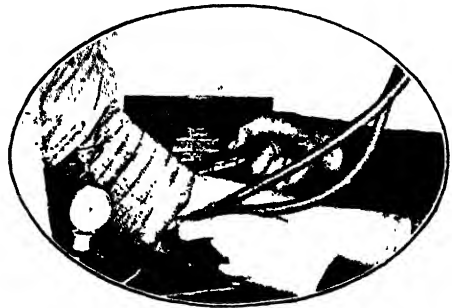
The pressure depends mainly on the contractile power of the heart and the peripheral resistance. The latter de-

pends on the caliber as well as the distensibility of the vessels.

Obviously, the systolic pressure approximates the intraventricular pressure, while the diastolic pressure represents the peripheral resistance. The pulse-pressure, or difference between the two, represents the head pressure driving the blood on out through the arterioles, *c.g.*:—

Systolic, or maximum .....	150 mm. Hg.
Diastolic, or minimum .....	120 " "
Pulse-pressure .....	30 " "

**Discussion of Pulse-pressure and Diastolic Pressure.**—Various figures



5. Tycos aneroid sphygmomanometer.

have been given for the normal range of pulse-pressure:—

Erlanger .....	30 to 45 mm. Hg.
Hirschfelder .....	30 to 40 " "
Young .....	25 to 30 " "

Lauder Brunton pointed out that the pulse-pressure depends on the pulse-rate. If the pulse is slowed more time is allowed for the blood to run through the arterial system during diastole. Diastolic pressure will be lowered and pulse-pressure increased. The reverse also applies.

A weak heart will not raise tension as rapidly as a strong one, and the time between the end of each systole and the next will be shorter and the pulse-pressure lower. In a stronger

heart the interval between systoles is longer and there is a larger pulse-pressure.

Now, turning to the blood-vessels, we find when contracting the diastolic pressure remains high, giving a small pulse-pressure, and *vice versâ*.

A low systolic pressure with a large pulse-pressure shows dilated vessels and a probably strong heart.

**Normal Readings.**—Before turning to the consideration of blood-pressure under abnormal conditions, let us consider the normal variations that have been determined by numerous observers. It is well to bear in mind the fact that blood-pressure standards cannot be absolutely fixed, being of considerable variation in different healthy individuals:—

	Age.	Systolic.	Diastolic.
Erlanger .....	19 to 25 years .....	110	65 mm. Hg.
Hirschfelder ....	All ages .....	115-120	75-85 " "
Janeway .....	Before middle life .....	100-130	25-40 mm. } lower than
	After middle life .....	130-145	25-40 " } systolic.
	Children before 2d year .....	75-90	
	Children after 2d year .....	90-110	
<i>Abnormal.</i>			Systolic.
	Before middle life, pressure above.....	145	mm. Hg.
	After middle life, pressure above .....	160	
<i>Normal.</i>			
Cook .....	Before 30 years .....	120-130	" "
	30 years on .....	125-140	" "
<i>Low limit.</i>			
Janeway .....	Male .....	100	" "
	Female.....	90	" "

A low systolic pressure with a slight pulse-pressure indicates the heart itself is weak; in addition, there is probably some dilatation of the vessels, though a feeble heart with normal vessels could give these signs.

If there is a high systolic pressure and a correspondingly high diastolic pressure, giving a normal pulse-pressure, we may assume there is a normal balance between heart and vessels, and a compensatory condition is present.

Thus pulse-pressure is of the greatest value in determining the condition present, whether mainly due to heart or arteries, and is most important in relation to treatment. By observing the changes in pulse-pressure of our cases under treatment we obtain the most accurate idea possible of the results that are being attained; far more so than when we utilize the systolic pressure alone.

In general it may be stated that females are about 10 mm. lower than males. The lowest blood-pressure readings according to Hensen were 40 mm. systolic, and lowest possible pressure with recovery was approximately 55 mm. Cook and Briggs consider 60 mm. systolic severe. Janeway, pressure below 75 mm. systolic rare except during operation, when it has reached 40 mm. The lower limit represents the resistance of the arterioles, due to the necessary vasomotor tone, and is probably never less than 50 mm. mercury.

**PHYSIOLOGICAL VARIATIONS IN BLOOD-PRESSURE.**—Where there are no pathological changes, the following factors affecting blood-pressure are to be taken into account:—

**Location of Cuff.**—It is important that the constricting cuff shall be on a level with the heart; other-

wise, the correct reading is lowered or raised by the effect of gravity on the column of blood according to whether the constriction is above or below the heart level. If above, the readings will be too low; if below, they will be too high.

**Position of Patient.**—The position of patient in relation to the horizontal is also important, systolic pressure being 8 to 10 mm. higher in the reclining than in the sitting posture.

There is about the same difference between sitting and standing posture. The diastolic pressure also rises but relatively higher than the systolic, and as a result pulse-pressure is decreased. The pulse-rate is also increased. The main point is, therefore, always to take subsequent readings on the same patient in the same posture, when possible.

**Meals.**—There is a moderate rise in systolic pressure and pulse-pressure after meals, and the pulse-rate is increased.

**Breathing.**—Deep and forced breathing raises blood-pressure during expiration, often as high as 10 mm., and lowers it during inspiration.

**Sleep.**—During sleep the maximum pressure is lowered 10 to 20 mm., due to relaxation and vasodilation. The diastolic fall is most marked.

In 20 men and 20 women, the writer found the systolic pressure during sleep remarkably constant, *viz.*, about 95 mm. in the men, with but 1 case differing from the average by more than 5 mm. In women the average was about 88 mm. The pressure at night during sleep was quite independent of that during the day, the latter having been between 102 and 137 in the women. In women, the blood-pressure at night was somewhat lower in those whose pressure had been exceptionally high by day than among

those whose day pressure was normal. The night pressure in men must be regarded as definitely pathologic if it exceeds 110 mm. and in women 105 mm. Paul Blume (*Ugeskr. f. Laeger*, Aug. 31, 1922).

The changes produced by **physical training** consist of a decrease in standing pulse, a lower diastolic pressure, an increase in pulse pressure, a smaller difference in the reclining to standing pulse, and an increase in the standing systolic over the reclining systolic. V. T. Scott (*Milit. Surg.*, Sept., 1924).

**Exercise.**—Causes a rise in maximum (systolic) pressure, and an increase in pulse-pressure, the rate being also increased. If muscular exercise is severe, there may be a rise in blood-pressure of from 5 to 10 cm., depending on the amount of force exerted. If exercise is excessive and fatigue ensues, blood-pressure falls and the pulse-rate is slowed.

Report of observations made upon 500 applicants for aviation service. The readings were made with the men recumbent, standing, and after an average of 1600 foot pounds of work in 5 seconds. The average readings in recumbency: pulse rate, 85.4; systolic pressure, 127.7; diastolic, 84.1; pulse pressure, 42.2, and the lengths of the several phases averaged: first, 12; second, 24.5; third, 6.2, and fourth, 5.1 mm. Hg. After exercise the averages showed characteristic responses. The pulse rate averaged 112; systolic pressure, 145.4; diastolic, 90; pulse pressure, 54.1; first phase, 13; second, 33.5; third, 11; fourth, 7 mm. Hg, and the average recovery time was 4.4 minutes. The area of cardiac dullness was never increased by the exercise, while 69 per cent. showed an apparent decrease. The pressure tests gave some indication of myocardial weakness, but this was better shown by the change in the cardiac area after exercise, the dyspnea and the prolongation of recovery time to from



10 to 15 minutes. Similar findings were noted in 5 cases with palpable radial arteries. The conclusions reached were that the various blood-pressure findings alone were of relatively little importance in determining physical fitness, but that the added information given by some form of measured exercise was of definite value. The increase in pulse rate after exercise was not found of value. B. Smith (Jour. Amer. Med. Assoc., July 20, 1918).

#### **Nervous and Mental Stimuli.—**

Pain, anger, emotion, and mental effort stimulate vasoconstriction and cause a rise in blood-pressure, especially marked in minimal (diastolic) reading. The pulse is also quickened.

Blood-pressure is also affected by two pathological conditions, not in themselves diseases:—

The **role of emotions** is well shown by Dearhorn (Med. Record, Sept., 16, 1916), who states that it is only by repeating the measurements each minute (or each 2 minutes) for a half-hour or less, and on several successive days, care being taken in interpretation to avoid all known sources of high pressure, that a correct estimate may be obtained. He found that it raised by tones of unpleasantness, and notably by anxiety; that in some cases, but by no means all, it appears to be lowered by all relaxing and pleasurable sensations; that it is, in general, variable in adults as in children, even during old age; that the deliberate relaxation of the voluntary muscles readily and greatly lowers the pressure.

In observations made during 8 months in 20 subjects aged 36 to 40 years, at the front, the writer found that explosion of a large shell close at hand caused a distinct rise in the systolic, diastolic, and pulse-pressure, which returned to normal within an hour. Fatigue and overwork always lessened the pulse-pressure, and nearly always increased the diastolic. Blood-pressure measurements are considered to afford the best criterion of fatigue requiring

rest from active duty. P. Ménard (Bull. de l'Acad. de méd., Oct. 17, 1916).

1. **Edema.**—Here the reading may be too high, due to the pressure required to squeeze the fluid out of the tissues. Hensen reports in one case an error of 20 mm. Hg.

2. **Asphyxia.**—Here also we obtain an extreme rise of pressure, and in slighter grades of deficient oxygenation of the blood, a rise to a less degree.

This condition must be considered in diseases of the lung, laryngeal diphtheria, etc.

The experimental studies showed that during vomiting, there is sometimes, according to Brooks and Luckhard (Amer. Jour. of Physiol., Jan., 1915), a period of elevated pressure, but more frequently a sudden and enormous drop in blood-pressure with cardiac inhibition at the moment of emesis, always periods of great oscillations in the blood-pressure. These great and sudden oscillations of the blood-pressure may cause a rupture of the blood-vessels which would occur with the same pressure but with slower changes.

**Time Consumed in Taking Readings.**—If constriction is continued over vessel for one minute, one may get a possible rise of 5 mm. Hg. Continued compression may cause a rise up to 20 mm.

**Precautions.**—Take all readings on the same patient at the same time of day, preferably midway between meals. Have the patient in a comfortable position, with muscles relaxed, best reclining, but in any case make all subsequent observations in the same position. Exclude all excitement, and see that patient is mentally composed and breathing quietly. Make the determinations as rapidly as possible. If the above precautions are observed, from a clinical

standpoint there will be no important error in the pressure values, providing the apparatus is accurate and the auscultation method properly employed.

The **diurnal variations** in arterial pressure should be taken into account when clinical readings are taken at intervals to obtain a correct estimate of the progress of a given case.

Thus, Weyse and Lutz, in an investigation of the diurnal variations in arterial blood-pressure, found that a rise of maximum pressure averaging 8 mm. Hg occurs immediately on the ingestion of food. A gradual fall then takes place until the beginning of the next meal. There is also a slight general rise of the maximum pressure during the day. The average maximum blood-pressure for healthy young men in the neighborhood of 20 years of age is 120 mm. Hg. This pressure obtains commonly one hour after meals. The higher maximum pressures occur immediately after meals, and the lower, as a rule, immediately before meals. The range of maximum pressure varies considerably in different individuals, but the highest and lowest maximum pressures are practically equidistant from the average pressure of any one individual. The minimum blood-pressure is very uniform throughout the day, and is little affected by the ingestion and digestion of meals. When it is affected, a rise or a fall may take place. There is a tendency for a slight general lowering of the minimum pressure throughout the day. The average diastolic blood-pressure for healthy young men in the neighborhood of 20 years of age is 85 mm. Hg. Thus the authors get an average pulse-pressure of 35 mm. Hg. Pulse-pressure, pulse-rate and the relative velocity of the blood flow are increased immediately on the ingestion of meals. They attain the maximum, as a rule, in half an hour, and then decline slowly until the next meal. There is a general increase in each throughout the day.

As to the **significance of variations**, in addition to those given above, Newman and Fischer believe that a fall in blood-

pressure associated with decreased pulse-pressure is indicative of *heart-failure*, whereas a fall in pressure associated with increased pulse-pressure is indicative of *hemorrhage* or *shock*. Slight changes in the systolic and diastolic relation are not to be relied on. Cases should be observed frequently in order that the state of the circulation be understood.

In *infectious diseases*, according to Schwartzmann, a high diastolic blood-pressure indicates a tendency to paralysis of the larger abdominal vessels with accumulation of the blood in them, and hence this must be accepted as a sign of the severity of the infection. A lower systolic pressure with a lower diastolic pressure is not a sign that the heart is weakening, but only that the vascular tonus is growing less. On the other hand, when the diastolic pressure rises while the systolic falls, the heart is weakening.

In a study of 43 tuberculous patients seen by F. C. Smith, the **effect of altitude** on blood-pressure was not great. The results failed to support the contention that hemoptysis depends on high systolic pressure. It seems extremely doubtful whether moderate altitude has any pronounced effect on tuberculosis. P. Schrumph maintains that many patients with circulatory troubles are actually benefited by a stay at an elevation of 2000 meters or less. The usual argument against altitude, that the blood-pressure will be raised as the atmospheric pressure becomes less, he regards as fallacious. Normal pressure is unaffected by an ascent to 2000 meters. In patients with slight or marked arteriosclerosis and hypertension, but without serious renal disease, he always found a fall in pressure.

Experiments on cats in which either **heat** or **cold** representing a difference of 25° C. above or below the body temperature was applied outside of the abdomen for 15 minutes. **Cold** produced little or no effect, while **heat** caused a material elevation in the blood-pressure, maintained throughout its application. F. S. Hammett, E. W. Tice, and E. Larson (Jour. Amer. Med. Assoc., Feb. 24, 1917).

The effects of **tobacco** in cigarette and cigar smoking were found by

the writers to correspond. There was an average increase in pulse rate of 13 beats per minute. Whereas the risk from any elevation in blood-pressure increases greatly the higher the initial pressure in the patient, it is undesirable for anyone having a constant systolic pressure much above 200. to smoke. Again, smoking is equally undesirable for anyone having a constant initial pressure above 160 mm. when the use of tobacco is found uniformly to produce a considerable rise in blood-pressure. Thompson and Sheldon (N. Y. State Jour. of Med., Feb., 1917).

**Mental work** causes an increase of blood-pressure and pulse rate, independently of emotional factors. In combined mental and muscular work the increases in pressure and pulse rate are generally greater than in mental or muscular work performed singly. R. D. Gillespie (Jour. of Physiol., May, 1924).

The rise in blood-pressure in **high altitudes** must be due to oxygen deficiency, for it can be obviated in many individuals by augmenting the oxygen tension. In spite of the rise in blood-pressure the arterial blood may show a normal oxygen tension; the point actually influenced is the tissue of the vasomotor center. Grossmann (Zeit. f. klin. Med., Aug. 20, 1925).

The effects of **sleep** on blood-pressure were studied in detail in 25 patients for a period of 38 nights. At the 4th hour of sleep there was observed the minimum systolic level—101 mm. Hg. Before waking there was a slight rise, and after waking an abrupt rise to the same level as had been noted in the 1st hour of sleep. A similar but less marked fall in diastolic pressure took place during sleep. The pressure curve is almost similar to the curve of the pulse rate. The fall of the pressure is ascribed mainly to the fall of pulse rate, although peripheral relaxation is probably also somewhat of a factor. Blankenhorn and Campbell (Amer. Jour. of Physiol., Sept. 1, 1925).

**BLOOD-PRESSURE IN DISEASE.**—Blood-pressure in disease may be either high (hypertension) or low (hypotension).

**HYPERTENSION.**—First considering hypertension, we find that, where it is not due to the factors we have just considered, or secondary to drugs, as adrenalin, strychnine, ergot, digitalis, etc., there is an increased peripheral resistance in the blood-vessels, which has been found to depend largely on the splanchnics. Another important point is the fact that continued high pressure cannot be maintained without cardiac hypertrophy, and that the increased tension will of itself cause changes in the vessel wall, thickening of intima and media, and loss of elasticity, with danger of rupture.

Out of 500 patients with definite endocrin disturbances, the writer found 40 who had systolic blood-pressures over 160. A surprisingly high number of endocrin cases treated for their glandular disorders were relieved of their hypertension. Some had lived for years disregarding it. Many cases heretofore described under such terms as the prealbuminuric stage of Bright's disease, latent arteriosclerosis, pre-arteriosclerotic hypertension, pure hypertension, benign hypertension, etc., are related to ductless gland dyscrasias. Of these cases of hypertension the highest percentage was found among the polyglandular cases. In 12 per cent. the pituitary and thyroid were differentiated as being most frequently associated with hypertension. A considerable number of cases of hypertension occurring at the menopause were due to glandular disturbance. Most cases responded to treatment directed entirely to the glandular state. Engelbach (Med. Rec., May 8, 1920).

The author gave patients  $2\frac{1}{2}$  liters (quarts) of fluid every 3 hours. Among other findings, a steady rise of blood-pressure was observed, in 1 man from

160 to 280. In 1 patient large amounts of water were passed, and the blood-pressure was not affected. J. L. Miller (N. Y. Med. Jour., Apr. 6, 1921).

Hypertension is apparently not a factor removal of which is essential to the individual's well-being. Essential hypertension is common and in its early stages is not associated with kidney involvement. As hypertension persists, however, secondary changes occur. Focal infections should be looked for. H. O. Mosenthal (Med. Clin. No. Amer., Jan., 1922).

In 67 cases the writer found, aside from heredity and environment, the following conditions as possible causes of hypertension: Arteriosclerosis, 10 patients; syphilis, 1; endocrin disturbances, 11; nephritis, 16; oral infections, 18; nasal infections, 4; tonsillar infections, 3; cholecystitis, 4. F. C. Rinker (Va. Med. Mthly., Mar., 1922).

The actual blood-pressure raising power belongs to the lecithin of the adrenal cortex—an excitant lipid. Pharmacology and clinical experience have long verified the fact that lecithin is a powerful stimulant of the cardiac systole and of general vascular tone, as well as an energetic promoter of general nutrition. Persistent dosing with adrenin may cause a marked, though gradual, rise of blood-pressure. As a rule, the cause of arterial hypertension in endocrin cases is to be found in toxic products due to inadequate katabolism of both tissue and food wastes. C. E. de M. Sajous (Amer. Med., June, 1923).

In a study of the relationship of *protein food* to high blood-pressure, the writers obtained negative results. In progressive nephritis with high pressure, reduction of protein intake sufficient to reduce the non-protein nitrogen and urea in the blood did not lower the pressure. In hypertension with slight or no renal impairment, the marked variations in pressure observed bore no relation to the intake of protein food, and no damage to renal function nor increase of non-protein nitrogen or urea of the blood was found to follow protein feeding up

to 150 Gm. daily. S. Strouse and S. R. Kelmian (Arch. of Int. Med., Feb., 1923).

Protein foods do not increase blood-pressure. *Starchy foods* may increase it indirectly by bringing on obesity. There is no definite evidence in the literature that sodium chloride raises blood-pressure. The level of the blood chlorides bears no relation to blood-pressure. Ingestion of 10 Gm. of salt failed to raise the pressure in cases of hypertension. H. O. Mosenthal and J. J. Short (Amer. Jour. Med. Sci., Apr., 1923).

Hypertension is a chemically produced effect of endocrin disease or disturbance. Evidence tends to show that the condition is initiated in or near the pituitary body. If there is a widespread impairment of endocrin functions, however, the pressure is, as a rule, very low. Nephritis, as well as chronic gonad disease in women, may likewise cause a chemical hypertension. Indeed, a rise of blood-pressure is one of the earliest signs of the impending climacteric. The menopause was the cause of the high pressure in 47 per cent. of 130 women examined. Effectual treatment of mild obesity by diet in 297 cases led to a definite reduction of blood-pressure in 37 per cent. of the men and 38 per cent. of the women. A. Faber (Ugeskr. f. Læger, Feb. 21, 1924).

The *guanidin bases*, compounds included in the "non-protein nitrogen" of the blood, exert a powerful pressor effect. In dogs the blood-pressure was often doubled or even tripled within a few minutes after injections of methylguanidin sulphate, and the rise of pressure often persisted for 4 to 5 hours. This effect was promptly annulled by slow intravenous injection of a solution of calcium, potassium and ammonium chlorides or of normal hydrochloric acid. While normal persons and afebrile patients with normal blood-pressure showed an average daily excretion of 100 mgm. of guanidin bases, patients with high blood-pressure, whether of the essential or the nephritic type, showed a decreased

output of these bases. R. H. Major (Jour. Amer. Med. Assoc., July 12, 1924).

Chronic *intermittent* hypertension is the adult and senile manifestation of a vascular neurosis. Pronounced pressure variations during the day are revealed by blood-pressure readings every 20 minutes. In the daytime the normal range of variations is 15 mm. Hg, while at night a reduction of pressure by not over 25 mm. may be considered normal. L. Hahn (Zent. f. inn. Med., Jan. 3, 1925).

Anrep and Starling had shown experimentally that reduction in the amount of blood reaching the part of the brain concerned with vasomotor control brings about a compensatory rise in the systemic arterial pressure. The writers found arteriosclerosis in the medulla oblongata without exception in cases with a history of hypertension, whereas the arterioles in this region were found unaltered when there had been normal blood-pressure. Suggestion that a localization of arteriosclerosis in the medulla may be the essential factor in persistent high blood-pressure. J. Bordley and B. M. Baker (Bull. Johns Hopk. Hosp., Apr., 1926).

### DISEASES WITH HYPERTENSION.

—**Arteriosclerosis.**—Here our diagnosis of the existence of sclerosis rests on the palpation of hardened vessel walls, visible tortuosity, or we may reason it is present from the sclerosed vessels in the eyeground, the enlarged left ventricle, ringing aortic second sound, and high blood-pressure.

Numerous observations have shown that unless the splanchnic vessels are affected there is not likely to be an increased blood-pressure and hypertrophy of the heart, but whenever the splanchnics are sclerosed the blood-pressure is increased:

In this condition the systolic pressure is usually increased (150-170 mm. to 250 mm.). The diastolic pres-

sure increases (110-130 mm.), but not proportionately, increasing the pulse-pressure greatly (60 mm. or over).

When the diastolic blood-pressure is not raised above 90 mm. Hg, there exists no vascular degeneration, however high the systolic reading. There are, however, 3 classes of exceptions to this: (1) marked aortic regurgitation; (2) severe mitral regurgitation with considerable cardiac hypertrophy; (3) an indefinite group found in people past middle age or of advanced years, who, notwithstanding the fact that their vessels are markedly thickened and systolic pressure is high, exhibit a normal or nearly normal diastolic pressure. Thorne (Pract., Nov., 1918).

If a hypertension persists, one may expect to be able sooner or later to demonstrate that (1) changes will occur in the larger vessels—arteriosclerosis in a clinical sense; (2) the heart will hypertrophy and become insufficient—myocarditis ensuing; (3) renal insufficiency will appear—chronic nephritis developing. This actual sequence occurs in some cases; in others it is different, but the end stage is the same. The progression may be stopped by death at any time, when there may be hypertension with arteriosclerosis and little else, or with chronic myocarditis, but no real nephritis; or chronic nephritis without actual cardiac insufficiency. H. A. Christian (Wisc. Med. Jour., Feb., 1922).

“**Angiosclerosis**” is a term which has been applied to a class of patients who have a permanent high blood-pressure with no signs of sclerosis or nephritis, even upon repeated examinations. Janeway associated it with an early chronic interstitial nephritis.

Its early discovery is very important in order to prevent cardiac hypertrophy and vascular changes, which are inevitable if the condition of high tension is not relieved.

It is important to regulate the diet, eliminate as far as possible overwork

and worry, and keep the bowel function active. Sweating is also of value.

**Essential hypertension** is a term now more commonly employed, and which has largely displaced Allbutt's original appellation **hyperpiesia**, referring to a condition of persistent primary high blood-pressure independent of arteriosclerosis. The cause of essential hypertension is not precisely known. It is presumed to represent, in particular, an arteriolar spasm due to toxic or nervous influences or both. A familial predisposition to arterial hypertension may exist.

*Essential hypertension* is to be considered, according to E. Kylin (Klin. Woch., Nov. 5, 1923), as a manifestation of disorder of the vegetative nervous system, probably secondary to defective endocrin functioning. There are various features which support this view. Thus, there is a marked instability of the blood-pressure, with extensive daily variations and great reductions upon rest in bed. Most cases also have a low carbohydrate tolerance, sometimes passing into diabetes. There are changes in the leukocytic picture (increase of mononuclears and eosinophiles) suggesting a vegetative neurosis. The blood sugar curve upon injection of adrenalin is flattened, and the pressure response is abnormally slight. There are analogies with bronchial asthma (the eosinophilia, adrenalin response, familial tendency), with which the condition is frequently combined. Seemingly slight stimuli, ordinarily inconsequential, are capable of causing abnormally great rises of blood-pressure by exciting vasoconstriction. The disturbance often occurs in association with the climacteric.

As symptomatic manifestations in 48 cases of essential hypertension, the writer was more especially impressed with morning headache, migraine after adolescence, dizziness and rheumatic pains mainly attending changes in the weather, lassitude (sometimes confined to 1 limb), discomfort in high temperatures, and occasionally palpitations. Kauffmann (Münch. med. Woch., Sept. 5, 1924).

The cases of essential hypertension are incommenced by heat, whereas the nephritics are fond of it. In most of the essential cases the blood-pressure showed a paradoxical rise in a warm room, while in some nephritics it showed a decrease. F. Kauffmann (Zeit. f. klin. Med., Oct. 25, 1924).

In 20 cases of essential hypertension, with pressures of 180 mm. or over, the basal metabolism was found regularly increased from +13.3 to +54.9 per cent. Of nephritic cases of high pressure, only a portion had a high metabolic rate, while in 2 cases of syphilitic aortitis it was normal. J. Mannaberg (Wien. klin. Woch., Mar. 1, 1924).

Basal metabolic rate often found increased in essential hypertension and nearly normal in nephritic hypertension. M. Händel (Zeit. f. klin. Med., Oct. 25, 1924).

**Nephritis.**—Chronic interstitial nephritis gives a high systolic pressure (200 mm. or higher) and a relatively low diastolic pressure, causing a large pulse pressure (60 to 80 mm. Hg).

Here hypertension is one of the most important signs, often making the diagnosis in obese individuals, where the enlargement of the heart is hard to define and the urine negative for a long time.

In patients with hypertension and presumably chronic interstitial nephritis, large amounts of fluid may cause a very decided increase in blood pressure, according to the promptness with which the kidneys excrete water. In 3 cases studied, large amounts of fluid daily for 6 days did not affect the urea nitrogen in the blood. In 2 of these, blood uric acid was definitely lessened, perhaps due to treatment. Miller and Williams (Amer. Jour. Med. Sci., Mar., 1921).

Janeway said: "Given a systolic pressure of over 200 mm., the diagnosis of contracted kidney must be disproved by repeated examinations before it is abandoned."

**Caution.**—If the heart has failed to compensate, the pressure may be low, and it is here that the pulse-pressure will aid materially. In this condition the pulse-pressure is lessened.

The prognosis depends not so much on the actual height of the mercurial column, but as to whether the pressure is rising or resistant to treatment. The ultimate danger is rupture and apoplexy.

Various data tend to show that there is no direct connection between the blood-pressure and morbid conditions in the kidneys, although abnormal conditions in both are almost invariably found parallel. There is much to sustain the assumption that an abnormally high blood-pressure is the primary disturbance, arteriosclerosis and vascular kidney affections occurring only secondarily. Hypertension is not, however, easily influenced. Moderate hypertension may subside under bed-rest and diet, but a high blood-pressure, 200 to 250 mm., never goes down permanently to normal; 170 mm. seems to be the extreme limit with which this is possible. V. Bie (*Ugeskrift for Læger*, Mar. 4, 1915).

#### **Chronic Parenchymatous Nephritis.**

—In it the blood-pressure is uncertain, often being normal. When there is hypertension it often aids, but its absence does not negate the diagnosis.

**Acute Nephritis.**—The pressure varies greatly, in typhoid fever and pneumonia there being no increase in tension. In scarlet fever, however, there is a sharp, sudden rise, often of 50 mm., and it is a valuable aid to the diagnosis.

**Uremia.**—Here blood-pressure runs parallel with the symptoms, maximum pressure being very high, in some cases 290 mm. Hg.

Pressure falls with the alleviation

of the symptoms as a general rule, though it may fall before fatal termination, due to failure of the heart.

**Apoplexy; Cerebral Thrombosis; Depressed Fracture of the Skull; Fracture of the Base; Intracranial Hemorrhage; Tumors (Rapid-growing, Cerebral); Jacksonian Epilepsy (Cases of Increased Intracranial Pressure).**—In these conditions of increased intracerebral pressure the highest blood-pressure readings occur; Hirschfelder gives systolic 300 to 400 mm.; diastolic 160 mm. or over; pulse slowed.

The high pressure is compensatory, and is the effort to supply more blood against increasing intracerebral tension, and thus prevent anemia of the brain.

The important point is not to bleed, and try to lower the pressure, but to operate where possible, and where not give atropine to paralyze the vagus, and allow the pressure to rise more rapidly.

In a case of head injury the blood-pressure reading is of great value; for in concussion the pressure is low, where in the above-named conditions it is invariably high, unless very late when cerebral paralysis has developed.

**Angina Pectoris.**—There are a large number of patients complaining of mild anginoid symptoms, tightness under the sternum, dyspnea on exertion, and belching after meals, which are accompanied by high blood-pressure. These are cases of mild angina pectoris. Given anginoid symptoms with marked hypertension (systolic 180 mm. or over) you are probably dealing with angina pectoris.

**Aortic Regurgitation.**—Here is found a systolic pressure 75 to 100

per cent. higher than the diastolic, the pulse-pressure being very high.

The pressure in some equals systolic 170 to 220 mm. Hg, diastolic 60 to 140 mm.; in other cases often systolic 120 to 130 mm., diastolic 50 to 60 mm.; but in all cases the pulse-pressure is great.

When you auscult over the artery in taking the blood-pressure reading you note a continuance of sound, so that the diastolic pressure in this case has to be determined by palpation.

Dr. Leonard Hill showed that in health blood-pressure is about the same in the brachial and femoral arteries, but in aortic regurgitation the readings from the femoral are much higher.

When the relation of pulse-pressure to the diastolic reading is low, in a doubtful case, it is not likely that there is aortic insufficiency.

#### **Chronic Cardiac Hypertrophy.—**

Here we have an increase in both systolic and diastolic pressures (systolic 140-160 mm. Hg; diastolic 90 to 110 mm. Hg).

**Cardiac Valve Lesions Other than Aortic.**—Blood-pressure in these cases is about normal when compensation is good.

**Heart with Loss of Compensation and Asthma.**—Here is found high tension from associated asphyxia, when severe actual edema of lungs takes place and life is in danger; the blood being loaded with carbon dioxide immediate relief must be given, *e.g.*, bleeding, amyl nitrite, nitroglycerin, and later, after acute condition is relieved, give cardiac stimulants.

**Myocarditis.**—On exertion there is often an initial rise of blood-pressure, not well maintained, falling during

continued moderate exertion. In severe cases of myocarditis pressure often falls from the beginning. This is a very good means of determining the condition of the heart muscle. Take the pressure reading, then give mild exercise, taking several blood-pressure readings and compare with the level observed before exercise was begun.

In addition there are myocarditis cases of large, weak hearts with dyspnea, edema, and subjective symptoms: 1, with hypertension; 2, without hypertension. 1. These are cases secondary to Bright's disease or arteriosclerosis, or are primary myocarditis cases which have developed Bright's. 2. These are primary uncomplicated cases of myocarditis or the terminal stage of the secondary type. The primary cases usually show a high normal blood-pressure, and are more liable to have edema (systolic 135 to 145 mm. Hg).

**Acute Endocarditis.**—It is associated with a low systolic pressure.

**Bradycardia.**—Here the pulse-pressure is increased.

**Idiopathic Epilepsy.**—It is associated with a slow pulse and a high blood-pressure, which falls with the termination of the attack, and is an aid in the differential diagnosis of the postepileptic state and uremia, where there would be a maintained pressure during coma.

**Gout** gives increased tension both during the attack and also between attacks, when arterial changes are marked.

**Plumbism.**—Both acute and chronic cases show a well-marked high tension. In doubtful cases, where there is high tension, examine for signs of plumbism.



**Exophthalmic Goiter.**—Blood-pressure is variable, but as the disease is often accompanied by a hypertrophied heart the systolic pressure is often raised, *e.g.*, systolic 140 to 160 mm. Hg; diastolic 90 to 110 mm. Hg; pulse-pressure 30 to 50 mm. Hg; pulse-rate 120 or more.

**Eye Disease.**—In primary glaucoma tension is markedly increased, but not in secondary glaucoma, making a good differential diagnosis. Arterial hypertension is often a cause of early retinal and arterial changes in the eye.

It is often of the greatest value to determine high blood-pressure in eye work, for in cataract enucleation with high blood-pressure postoperative interocular hemorrhage and blindness can be prevented by a preliminary bleeding which will reduce the tension for a few days, allowing the eye to accustom itself to its new condition. Also by proper treatment advancing ocular changes may be prevented when associated with high tension.

**Obstetrics.**—Most authorities agree that at the end of pregnancy there is normally a rise in systolic blood-pressure (10 to 15 mm. Hg), with little change in the diastolic; although Starling, who reported the results of cases over a five-year period, believes the blood-pressure remains normal.

A fact recognized by all authorities is that the toxemia of pregnancy in the later months is accompanied by a rising blood-pressure, and that it is often present some time before any other signs or symptoms.

In pregnancy the following figures have been given for normal cases: Starling, systolic pressure, 110 to 120 mm. Hg. J. C. Hirst, systolic pres-

sure up to 7½ months, 118 mm. Hg; middle of last month, 124 mm. Hg.

The whole subject is well summarized in a paper by the above writer, in which he says:—

"1. Normal blood-pressure in the non-pregnant is 112 mm.

"2. Normal blood-pressure in the healthy pregnant is 118 mm.; in the last month slightly higher.

"3. Blood-pressure in toxemia in the first half of pregnancy associated with pernicious vomiting is invariably low.

"4. Blood-pressure in the toxemias in the latter half of pregnancy associated with albuminuria and eclampsia invariably high.

"5. High and rising blood-pressure is an invariable and early, often the earliest, sign of toxemia in the latter half of pregnancy.

"6. Upon rupture of the membranes there is an immediate fall of pressure,—60 to 90 mm. This fall is temporary only, but is attended with marked relief in headache and epigastric pain these patients so often complain of. Relief lasts for some hours, during which there is a gradual return to the previous level.

"7. There is a second fall (60 to 90 mm.) after the child is born. This again is temporary and is 15 to 30 mm.; if the patient has not bled profusely, the pressure is back to somewhere near the previous level before birth.

"8. Usually blood-pressure is high for forty-eight hours after birth, then begins to subside and reaches normal (118 to 124 mm.) in seven to ten days.

"9. A blood-pressure below 125 mm. should be disregarded; 125 to 150 mm. needs careful watching and moderate eliminative treatment. Over

150 mm. needs active eliminative treatment and probably will, especially if there is a tendency to climb higher, require induction of premature labor."

Starling, in treatment, advocates, before using more drastic methods, **rest in bed on a carbohydrate and milk diet**, with 1 teaspoonful of **sodium bicarbonate** four times a day, and 4 pints of liquid and **thyroid extract** in sthenic cases.

The blood-pressure remains high, after delivery and the relief of toxic symptoms, where there has been a previous nephritis. Hypotension also is important after delivery, in relation to the question of hemorrhage and shock, being marked in both of these conditions. Whether the pressure is stationary, progressively rising or falling is of more importance in relation to treatment than absolute figures, though the latter serve as a good guide.

#### **Therapeutics of Hypertension.—**

The first and most important thing to regulate is **diet**, both as to amount and character of the food, avoiding animal proteins; to see that elimination is good; to be careful to look into and regulate the amount of mental and physical strain; in a word, to attend to **general hygiene**. Smoking and alcoholic beverages should be stopped. If this treatment is not sufficient, use **potassium iodide** in small doses.

Do not be in a hurry to lower tension in all cases, as it is often compensatory.

In cases of high tension with discomfort, as pain and tightness across the chest, Mackenzie used potassium iodide in 5-grain doses four times a day, and found that it often relieved

the symptoms quite frequently without lowering the tension. He also advocated **chloral hydrate** in 5-grain doses two to three times a day, as well as in larger doses to produce sleep, especially in cases of angina pectoris.

In addition, the patient should **eat slowly**, with a twenty-minute **rest after meals**; use **blue mass** or **calomel** occasionally; use **digitalis** if the high tension is due to failing compensation, as it will restore the heart tone; in severe cases use **absolute rest** with **massage**. Rest, mental and physical, as in heart disease, is the most valuable means of treatment. In toxic cases treat, with active **purgation**, **hot-air baths**, etc.

R. D. Rudolf recommends, when these means have failed and there are symptoms of cerebral trouble, the use of **bleeding** or vasodilation; **amyl nitrite**; **nitroglycerin**, doses of  $\frac{1}{100}$  gr. (action lasts one hour, tolerance soon formed); **sodium nitrite** (freshly prepared), 2 grains (action lasts two hours, no tolerance acquired); **erythrol tetranitrate**,  $\frac{1}{2}$  grain (action lasts six hours, no tolerance acquired).

In addition we may use **thyroid extract**, 2 to 3 grs. *t.i.d.*; **high-frequency electricity**, unreliable and effect often transitory; **baths**, not much permanent effect, though a series may give a fair result, as they reduce toxemia.

Extensive experience has led F. de Havilland Hall to treat high pressure cases as follows:—

For patients with a pressure of 200 mm. Hg and upward, overworked mentally and physically, treatment should begin with a period of **absolute rest**—especially if there be a pulse of over 100 per minute.

Many of the cases of high pressure occur in people who take too little exercise. **Walking** is one of the best exercises to be ordered. **Golf** may be allowed to nearly all

except those with advanced arteriosclerosis. The **methods of Schott and Oertel**, if used, should be carried out under the direction of physicians with special experience in this line. Hall has found **massage** extremely useful in patients unable to take sufficient exercise; it should be almost entirely confined to the chest and extremities.

**Warm baths, followed by vigorous friction** of the skin, are very beneficial. If the patient has been accustomed to Turkish baths, he may continue their use.

In case of *insomnia* the **wet pack** at 70° F. often has a very soothing effect.

The **electric light bath** is very useful in many cases, stimulating the cutaneous vessels and causing sweating.

From the **Nauheim treatment** this author has seen great benefit in suitable cases, but it is contraindicated in advanced arteriosclerosis, chronic nephritis, and intrathoracic aneurism. It should be carried out only under a physician with special experience.

A period of starvation benefits some patients, while in some cases it is difficult to induce the patients to take sufficient nourishment. Speaking generally, the most suitable diet is one mainly composed of **vegetables, farinaceous articles and milk**. In some dyspeptics  $\frac{1}{2}$  pint (250 c.c.) of **soured milk** may be taken 3 times daily, with great benefit. Hall **limits** the amount of salt taken as much as possible, and prohibits salted meat and fish. Supper should be a light meal—a little fish and vegetable with a milk pudding, for instance.

The condition of the gums and teeth needs careful attention, pyorrhea being one of the causes of high tension.

**Calomel and blue pill** are useful not only as aperients, but also have a remarkable effect in lowering blood-pressure. A teaspoonful of **Epsom or Glauber's salts** may be taken in half a tumblerful of warm water before breakfast, or one of the mineral waters. A tablespoonful of pure **paraffin** at night acts pleasantly.

Next to the aperients come the **iodides**. Some patients tolerate the **sodium salt** better than that of potassium. If neither seems to suit, **iodoglidine** may be tried. The author orders small doses—3 grains (0.2 Gm.) to be taken 3 times daily.

In patients with a *syphilitic* history the **Wassermann reaction** should be tried,

and, if positive, **mercury** administered, preferably by inunction, followed by **potassium iodide** in full doses.

High blood-pressure is often met with at the *menopause*, and is frequently accompanied by obesity; in such cases small doses of **thyroid gland**, together with a combination of **bromide and iodide of potassium**, are most useful.

If the iodides are badly borne **potassium** or **sodium nitrite** in 1- to 2- grain (0.06 to 0.12 Gm.) doses may be tried, though doses up to 5 grains (0.3 Gm.) have been warmly advocated. In solution they are unstable, so are best ordered in chocolate tablets. In *rheumatic subjects* **sodium salicylate** should be ordered.

The more powerful and quickly acting vasodilators, such as **amyl nitrite, nitroglycerin, and erythrol tetranitrate**, the author reserves chiefly for *anginal or dyspneal attacks* in those with high pressure. **Erythrol tetranitrate** in doses of  $\frac{1}{4}$  grain (0.016 Gm.) is most useful in patients who get anginal symptoms on starting to walk. It should be given  $\frac{1}{4}$  hour previously.

**Venesection** is indicated where the patient is unconscious and cerebral hemorrhage is feared; likewise in convulsive cases with high tension.

The effect of the **lowering of salt and water intake** upon patients with arterial hypertension not caused by obvious renal disease was tested by the writer in 7 cases. Rather pronounced reductions of both the systolic and diastolic pressures were obtained in 6 instances and slight reduction in the seventh. With the reduction in salt in such cases the desire for water is decreased. J. H. Musser, Jr. (N. Y. Med. Jour., Oct. 16, 1920).

From the d'Arsonval **high-frequency current**, the writers noted a slight but definite reduction in systolic and diastolic blood-pressures. The diathermic current caused a slight fall in systolic pressure. Bain, Edgecombe, Kidd and Miller (Lancet, Apr. 30, 1921).

The writer **reduces the protein intake** from about 50 Gm. (1 $\frac{3}{4}$  ounces) to about 30 Gm. (1 ounce) a day, according to body weight. A protein-free diet is inadvisable, entailing loss of weight and perhaps anemia. C. T.

Stone (Tex. State Jour. of Med., Feb., 1922).

**Lumbar puncture** performed on patients with extremely high blood-pressure often affords relief. N. B. Foster (Jour. Amer. Med. Assoc., Sept. 30, 1922).

The author orders salt restriction at intervals, with substitution of **bromides**. G. Singer (Med. Klin., Mar. 31, 1923).

In hypothyroidism with hypertension, **thyroid gland** restores the equilibrium. In the hypertension of the menopause, the same product, with **ovarian gland** and **corpus luteum**, is helpful. In the high pressure frequently attending hyperthyroidism the cause is usually a **focal infection**—cecal, tonsillar, dental, etc.—after removal of which the pressure recedes. The **salicylates**, **ergotin** and **quinine hydrobromide** also give good results in such cases. C. E. de M. Sajous (Amer. Med., June, 1923).

Injections of 0.02 to 0.04 Gm. ( $\frac{1}{2}$  to  $\frac{2}{3}$  grain) of **sulphur** claimed to have markedly lowered the pressure in 13 cases of arteriosclerosis or nephritis. S. Rusznyak (Orvosi hetil., Aug. 19, 1923).

Almost all of the writer's cases harbored **foci of infection**, removal of which resulted in definite blood-pressure reduction. In obese patients, restriction to a **low caloric diet** led to a pressure reduction nearly commensurate with the weight lost. D. R. Black (Jour. Mo. State Med. Assoc., Sept., 1923).

In a number of cases, including some of angina pectoris with hypertension and cardiac overstrain, **diathermy** gave persistent symptomatic relief. Brockbank (Lancet, Oct. 20, 1923).

**Salt restriction** is favored by the writer, who observed a reduction of pressure to normal in 6 out of 10 cases thus treated. The salt taken should be less than 0.5 Gm. a day. Even where the pressure is not reduced to normal, salt restriction relieves symptoms and avoids the danger of apoplexy. J. J.

Selman (Ohio State Med. Jour., Dec., 1923).

There is a group of cases featured by the combination of hypertension, hyperglycemia, obesity and arteriosclerosis. The treatment consisted of **avoidance of undue fatigue and effort**, and a diet yielding about 1600 calories and consisting of protein, 85 Gm.; carbohydrate, 125 Gm., and fat, 80 Gm. Usually the patient was allowed to "break training" as regards the diet for 1 or 2 days at 5 or 10-day intervals. At times, to promote weight loss, a **limited milk diet** was enforced every 5th or 7th day. All the patients lost weight and the systolic and diastolic pressures declined (about 25 to 50 mm. systolic). W. W. Herrick (Jour. Amer. Med. Assoc., Dec. 8, 1923).

**Sodium phosphate** or **magnesium sulphate** is best for bowel elimination. The **cabinet bath**, once or twice weekly, is useful. **Benzyl benzoate** is valuable to prevent anginal or cerebral crises. W. J. Stone (Cal. State Jour. of Med., Dec., 1923).

In the **arterial spasms** of essential hypertension as well as angina pectoris, intravenous injection of 10 c.c. of 20 per cent. **glucose** solution advocated. In about  $\frac{1}{2}$  hour the blood-pressure is reduced, and in some cases it remains low for several days. Meyer (Schweiz. Arch. f. Neur. u. Psych., xiii, 440, 1923).

Alternate use of **potassium iodide**, **erythrol tetranitrate** and **guipsine** (a French preparation of the mistletoe, *Viscum album*), gave good results in arteriosclerosis with dizziness, dyspnea, oppression and angina pectoris. H. J. Vetlesen (Norsk Mag. f. Laeg., Feb., 1924).

**Digitalis** often lowers the blood-pressure in hypertensive cardiovascular-renal disease through the increased elimination by diuresis. The **theobromine** group of diuretics act similarly. A search for ductless gland influences should be made. F. S. Smith (Ann. of Clin. Med., May, 1924).

In 14 cases pronounced pressure reduction followed the giving of 3 drams (12 Gm.) of **calcium chloride** daily.

W. L. T. Addison (Can. Med. Assoc. Jour., Nov., 1924).

**Sodium nitrite intravenously** recommended. The author gives successive amounts of 0.005, 0.01, 0.02, and at times 0.03 or 0.04 Gm. ( $\frac{1}{12}$ ,  $\frac{1}{6}$ ,  $\frac{1}{3}$ ,  $\frac{1}{2}$  or  $\frac{2}{3}$  grain), in a 1 per cent. solution, in series of 15 injections, at first daily, then at 2- or 3- day intervals. Petzetakis (C. r. Soc. de biol., Dec. 27, 1924).

The blood-pressure is lowered by **benzyl benzoate** where it is of functional origin. Capuani (Policlin., Nov. 2, 1925).

**Hepatic extract** has been used clinically in hypertension by R. H. Major (Jour. Amer. Med. Assoc., July 25, 1925) and by W. J. Macdonald (Canad. Med. Assoc. Jour., July, 1925, and Boston Med. and Surg. Jour., Mar. 4, 1926). The extract, as described by Major, has a marked depressor effect in certain cases, contains very little protein, and possesses no toxicity in the doses employed (3 to 5 c.c.—48 to 80 minims). On the normal blood-pressure of healthy persons these doses usually have no marked depressor effect. In all, 42 patients were treated, receiving the extract at intervals ranging from  $\frac{1}{2}$  day to 1 week. The effect was more prompt after intravenous injection, but was also obtained after intramuscular or subcutaneous injection. Within 1 hour after injection the blood-pressure usually falls by from 20 to 50 or even 70 mm. Hg. The fall is gradual and unattended by symptoms, except for slight dizziness in a few cases. In some the reduction persists only 2 to 3 hours, but it many it apparently continues 24 hours and sometimes several days. Several patients, after 8 to 10 doses, had a fall in blood-pressure persisting for 1 week or more.

**HYPOTENSION.**—Here we find, as a rule, not so much cardiac weakness as failure of the vasomotor center.

As regards the meaning of this condition, Cornwall has reached the following conclusions: 1. A low systolic pressure, with correspondingly low diastolic pressure, does not necessarily mean poor circulation; it does imply a diminished reserve power of the circulation. 2. A low systolic pressure, with comparatively high diastolic pressure, and therefore a small pulse-pressure, usu-

ally means myocardial weakness with chronic nephritis, arteriosclerosis, or arterial spasm, and may be prognostically bad. 3. A low diastolic pressure, with comparatively high systolic pressure, and therefore an excessively large pulse-pressure, may mean several things: A purely functional condition, a compensated aortic regurgitation, myocardial degeneration without arteriosclerosis or nephritis, toxemic irritability of the myocardium, or vasomotor dilatation from any cause. 4. The diastolic pressure seems to be more stable than the systolic, and to show less often marked variations from its normal, without definite pathological cause; the systolic pressure seems to accommodate itself to the diastolic more easily than the reverse. The diastolic pressure indicates the peripheral resistance, which in many cases is determined by permanent pathologic conditions. Increase of diastolic pressure beyond normal limits causes pulse-pressure to assume an overload if adequate circulation is kept up. 5. Vasodilator drugs may improve the circulation by increasing the pulse-pressure. 6. Cardiac depressant drugs may lower the diastolic pressure by diminishing the systolic force and calling for a pulse-pressure overload.

**Acute Infectious Diseases.**—These all have low tension except meningitis. The fall of pressure is mainly due to vasomotor depression or paralysis from the toxins, and, to a less extent, from a damaged heart muscle, due to the same cause.

**Typhoid Fever.**—Here we have one of the lowest pressures occurring in disease: Often the systolic pressure is 100 to 120 mm. Hg; the diastolic, 60 to 90 mm. Hg. The systolic has been as low as 75 mm.

The fall in pressure is gradual, and takes place progressively (Janeway), *e.g.*:—

First week,	systolic	115	mm.	Hg.
Second "	"	106	"	"
Third "	"	102	"	"
Fourth "	"	98	"	"
Fifth "	"	96	"	"

Here the value of routine blood-pressure observations is very great.

In hemorrhage there is a sharp, sudden fall, due to a lessened volume of blood. In perforation just the opposite sometimes takes place, the irritation of the peritoneum causing a reflex vasoconstriction and a sudden, sharp rise in blood-pressure. Briggs and Cook found in 1 case a rise of blood-pressure hours before there were any other definite signs of perforation. The diagnosis was confirmed by operation. As they showed, however, one cannot always expect such a rise of blood-pressure, for the vasomotor center may be exhausted. Thus, a lack of blood-pressure rise does not negate other evidences of perforation, but when present is reliable, unless pneumonia develops.

Using blood-pressure determinations with treatment, they found baths, when favorable, produced a rise in blood-pressure. Of the drugs strychnine and digitalis were the best to combat collapse. For a quick result, strychnine, gr.  $\frac{1}{10}$  to  $\frac{1}{20}$  hypodermically, was given, and the resulting rise in blood-pressure was maintained for an hour or so. When the pressure begins to fall, it may be maintained by a smaller dose.

Digitalin hypodermically was more certain than strychnine, with an initial dose of gr.  $\frac{1}{10}$ . Permanency of results may be obtained by combining the two drugs.

**Pneumonia.**—Here there may not be much change in the blood-pressure, though as the disease progresses there is a tendency for it to decline.

Hirschfelder: Systolic, 110 to 130 mm. Hg; diastolic, 90 mm. Hg; pulse-rate, 120.

Gibson, of Edinburgh, made a gen-

eral rule which seems to work out well, except in alcoholics: When the systolic pressure expressed in mm. of Hg is higher than the pulse-rate expressed in beats per minute, the condition of the patient is good; when it is lower, the condition is serious.

According to Lambert, blood-pressure in pneumonia is of the greatest value in determining whether the condition present is one of vasomotor paralysis due to toxins, in which case it is low; or whether the patient is suffering from high tension, with cardiac failure imminent.

About one-half the cases die of vasomotor paralysis, the other half from failure of the heart. In the one, adrenalin, camphor, strychnine, and digitalis are indicated; in the other, relief of the high tension with vasodilators or bleeding.

The matter has been tersely expressed by H. A. Hare: "If the vessels be at fault the difference between diastolic and systolic pressure will be marked, the heart if strong sending out a forcible wave of blood in an endeavor to fill the blood-paths. On the other hand, if the pressure be low from a failing heart, there will be little difference between diastolic and systolic pressure, for obvious reasons."

**Diphtheria; Acute Rheumatism; Scarlet Fever; Measles.**—These all show a slightly lowered blood-pressure. The systolic pressure usually falls below 100 mm. Hg (Weigert).

In scarlet fever, if acute nephritis develops, there will be a sharp rise—a good diagnostic point.

**Phthisis.**—Here we usually find a low systolic pressure: 90 to 100 mm., though it may vary between 80 and 120 mm.

Given a patient with tuberculosis, a falling blood-pressure is a bad sign, while a rising blood-pressure toward the normal is equally favorable.

When the blood-pressure has reached the normal and remained there, we may feel pretty confident our case is well; so that in supposedly cured cases it is important to take the blood-pressure observations to determine whether there is any recurrence of the disease.

Given a patient with a persistent low blood-pressure, always consider the probability of tuberculosis very seriously, especially where other causes for the low tension cannot be determined.

Lauder Brunton regards low tension as due usually to, 1, beginning phthisis; 2, excessive smoking; further stating that where smoking can be excluded always examine the lungs carefully for tuberculosis.

Dr. Haven Emerson warns us that persistent low tension should put us on guard to prevent tuberculosis, especially where the patient is under unhygienic conditions.

**Diarrhea; Dysentery; Cholera; after Profuse Vomiting, as in Carcinoma of the Stomach, Intestinal Obstruction, Peritonitis, etc.**—Here we find marked low blood-pressure, as the arteries are depleted of fluid. Here blood-pressure determinations are valuable in following treatment and as a means of determining impending shock or collapse.

**Cancer; Chronic Phthisis; Anemias, etc.**—There being associated brown atrophy of the heart as a consequence, there is low blood-pressure in all of these conditions, the systolic being 10 to 20 mm. lower than normal.

**Pericarditis and Acute Cardiac Conditions.**—Here pressure is low, the vasomotor center being depressed by the toxins of the disease, and there is also some weakness of the heart muscle. The systolic pressure varies from 98 to 140 mm.

**Acute Infections of Children.**—Here Briggs and Cook found blood-pressure determinations of the greatest value in prognosis and treatment. If pressure is falling there is danger of collapse and it is an indication for active stimulation.

They concluded that systolic pressures of 60 mm. during the first year and 80 mm. in older children were the danger lines calling for active stimulation.

*Treatment.*—In collapse with cyanosis they used a mustard bath, and found that strychnine and digitalis were the most reliable drugs.

*Prognosis.*—A short-lived response to treatment with a renewed fall is a bad sign.

**Syphilis.**—There is a hypotension during the acute stages due to the toxemia of the disease.

**Tabes Dorsalis.**—Pal concluded that with the lightning pains there was a marked fall in blood-pressure; in contradistinction to gastric crises, where there was an enormous rise. He assumed that as there was marked hypertension the splanchnics must be involved, and advised the use of chloral to relieve the condition, on account of its blood-pressure lowering qualities.

The association of high tension with gastric crises aids in a differential diagnosis, as there are only two other conditions of pain in the abdomen with high tension: 1, lead colic; 2 angina abdominalis of arteriosclerosis.

**Neurological Conditions.**—(a) *Melancholia* elevates blood-pressure in proportion to the symptoms, and is relieved by vasodilators, improvement occurring coincidently with the lowering of pressure.

(b) *General Paresis*.—Here in the early stage blood-pressure is normal, while in the late it is low.

(c) *Acute Mania*.—Here blood-pressure is low and after an attack lower still, due to exhaustion.

(d) *Trifacial Neuralgia* is accompanied by a high blood-pressure.

(e) *Insomnia* may be associated with either one of two conditions: 1, high tension (systolic 130 to 150 mm. Hg); 2, without high tension. In the first vasodilators act as hypnotics and are indicated; sleep takes place as the pressure falls. In the second class sulphonal, trional, and similar drugs are more effective.

(f) *Neurasthenia, Hysteria, etc.*—Pressure here is variable, but becomes high readily, owing to the nervous stimulation of the vasomotor center.

(g) *Alcoholic Delirium*.—Here pressure is lowered 30 to 40 per cent.; therefore we must use care in the employment of hot packs to quiet these patients, as we may cause collapse.

**Shock and Collapse.**—Here we have a very marked and dangerous fall in blood-pressure, due to vasodilation, from peripheral nerve stimuli to the vasomotor center. Henderson claims the vasomotor depression is due to overaëration and lack of carbon dioxide to stimulate the center. Here at times the systolic pressure has been as low as 40 to 60 mm. Hg.

Cook and Briggs proved that the

vasomotor center was not exhausted, for by the use of strychnine and digitalis they were often able to save apparently hopeless cases; that adrenalin intravenously will raise the pressure, but that its action is fugacious; that an intravenous saline injection is of no value to raise pressure unless adrenalin is added, and that  $\frac{1}{4}$  to  $\frac{1}{2}$  gr. of cocaine hypodermically will give an almost immediate rise of blood-pressure (10 to 20 mm.) and maintained from one to three hours.

**Extensive Hemorrhage.**—In this case there is a marked fall due to the loss of volume of blood. This condition is treated by intravenous saline injection, after the bleeding point is secured.

**Surgery and Anesthesia** (Briggs and Cook).—(a) *Ether* increases the blood-pressure in the first stage, reflexly from the irritation of the mucous membrane. During the second stage the pressure also rises, owing to the muscular activity. In deep anesthesia the pressure level falls to just above the normal.

(b) *Nitrous Oxide*.—Here there is a rise of pressure due partly to asphyxia. When used with ether there is an initial rise, but the second increase of pressure is eliminated, because the stage of muscular activity is avoided.

(c) *Chloroform*.—Blood-pressure falls from the start, and remains low, except in pregnancy.

If during anesthesia shock or collapse is imminent, there is a marked fall in blood-pressure before other signs are manifest; hence the value of taking blood-pressure readings every five minutes during the administration of an anesthetic. If pressure



*falls, correct any faulty administration of anesthetic; if the pressure then rises, proceed.*

If the pressure continues to fall, or remains at a dangerous level, use active measures, and terminate operative procedures as rapidly as possible.

**Spinal Anesthesia.**—This is generally attended with a decided reduction of blood-pressure.

**Operative Procedures.**—Cutting or manipulative procedures cause a transitory rise in blood-pressure of about 10 mm., due to the pain impulses conveyed to the vasomotor center; it may rise again, remain low, or fall farther to shock. If a local anesthetic is injected into the nerve-trunks during the operation there is less danger of shock.

Blood-pressure readings should be taken routinely before, during, and after operations. Before operation often a case has a high tension, which may become dangerous when an anesthetic is administered, unless it be lowered by preparatory treatment. After operation routine observations show the onset of shock or hemorrhage.

In pleural and peritoneal effusions, there is a rise of blood-pressure. Aspiration produces a fall, which can be determined by blood-pressure examinations, the aspiration being stopped if the fall becomes dangerous.

**Alcohol.**—In small amounts there is but little effect on pressure, but in any quantity there is a vasodilation and fall in pressure. Long-continued use leads to sclerotic changes and higher tension.

**Tobacco.**—Its moderate or occasional use produces a slight rise. When used to excess it produces low tension.

**Tea and Coffee.**—Both produce a transitory rise. Subjects who indulge freely often have a high tension, which leads to arteriosclerosis.

Distinct hypotension is compatible with perfect health. Most life insurance medical directors are convinced that hypotension in apparently healthy persons in middle life adds to the life expectancy. Persistent low blood-pressure occurs with certain chronic diseases, chronic infections, cachectic states, infantilism, myasthenia gravis, status lymphaticus and certain circulatory lesions. The real nature of "essential hypotension" is not yet understood; in some cases low-grade focal infections seem responsible. Hypotension also occurs in endocrin disturbances. Histamin and other vasodilators are constantly produced in the body; persistent hypotension in many conditions may be due to poisoning and dilatation of the *capillaries* by such substances. A. Friedlander (Jour. Amer. Med. Assoc., July 19, 1924).

The symptoms in patients with pressures below 100 mm. are very diverse and variable. The most important are exhaustion, inability to do prolonged or constant mental or physical work, restlessness, headaches, listlessness or apathy and digestive disturbances. Readings below 80 are very uncommon. L. A. Levison (Ohio State Med. Jour., Sept., 1924).

**Treatment of Hypotension.**—1. General hygiene and tonics.

2. **Hydrotherapy** is of some value, *e.g.*, needle bath, graduated from warm to cold; Vichy bath.

3. **Massage.**

4. **Exercise**, moderate and graduated according to needs.

5. **Laxatives**, where low tension is associated with constipation.

There are 2 types of low blood-pressure: The one due to congenital conditions ("diathesis" or "constitution"); the other due to endocrin exhaustion from infectious diseases or physical

exhaustion and exposure. The endocrins most usually affected are those of the genital sphere. The suprarenals occasionally show involvement, but more usually it is the thyroid, and still less frequently the pituitary. Treatment demands, in the congenital group, an explanation to the patients of the **mode of life** necessary if they are to be even relatively efficient. In the other group, a patient search must be made for **occult infections**, and if these can be **removed** and efficient **tonic therapy** instituted, the outlook is favorable. G. H. Hoxie (Mo. State Med. Assoc. Jour., Apr., 1921).

**Pituitary preparations**, particularly if given in conjunction with **adrenalin**, exert a more permanent hypertensive effect than the latter drug given alone. Pal (Med. Klin., Mar. 31, 1923).

In constitutional hypotension a general making-over of the patient is required. **Exercise**, especially **mountain climbing**, **massage**, a **sea voyage**, and **tonic medication** are usually beneficial. **Removal of all depressing factors and focal infections** is necessary. D. Riesman (Atlantic Med. Jour., May, 1924).

**VENOUS PRESSURE.**—In determining the pressure in the veins a manometer such as that employed for the measurement of the intraspinal pressure may be used. Thus, Villaret, Saint-Girons and Grellety-Bosviel (Presse méd., Apr. 7, 1923) use Claude's spinal manometer, connected with a needle by a rubber tube with a conical adapter (to fit in the needle) at one end and an interpolated piece of glass tubing. The tube is moistened with sterile olive oil to prevent clotting. The patient lies horizontally with the arm relaxed and on the same level as the body. The needle is passed into a vein and connected with the manometer, all compression proximal to the puncture being avoided. In adult males the normal venous pressure is 13 cm. of water and in females, 12 cm. Normally the venous pressure in water measures about the same as the arterial pressure in mercury (13 cm. Hg); the arterial is thus about 13 times greater than the venous.

The existence of heart disease, according to the above observers, is shown very early,

especially in aortic insufficiency, by a diminished ratio of the arterial to the venous pressure. In young individuals with high arterial pressure but normal arteries the ratio is generally normal. Where there are changes in the arteriocapillary system—arteriosclerosis, spasm, edema—venous pressure is low, this being usually the case in old subjects, with the exception that when cardiac decompensation sets in, it may become high. In lung disorders such as emphysema and tuberculosis, the venous pressure foretells the effects of the pulmonary condition on the right heart. The height of the venous pressure reflects to a great extent the degree of stasis existing in the right auricle.

Venous hypertension observed in auricular fibrillation, mitral disease, exophthalmic goiter, syphilitic aortitis and nephritis. In arteriosclerosis of the kidneys, however, this condition was absent. These results tallied largely with the electrocardiographic findings, which showed right ventricular preponderance in mitral disease and exophthalmic goiter, while in nephritis there was left ventricular preponderance. Tatterova and Serf (Casop. lek. cesk., Sept. 19, 1925).

With the subject recumbent and using the level of the auricle as base, the veins of the foot yielded approximately the same pressure as the ulnar vein. In the standing posture the hydrostatic pressure of the column of blood from the heart to the foot has to be superadded. Schott (Münch. med. Woch., Feb. 5, 1926).

PERCIVAL NICHOLSON,  
Ardmore, Penna.

**BLOOD TRANSFUSION.** See **VENESECTION**.

**BLOOD-VESSELS, DISEASES OF.** See various diseases of this class: **ANEURISM**, **ARTERIOSCLEROSIS**, **ETC.**, and **VASCULAR SYSTEM, DISEASES OF**.

**BLOOD-VESSELS, INJURIES OF.** See **VASCULAR SYSTEM: INJURIES AND WOUNDS OF VESSELS**.

## BLOOD-VESSELS, TUMORS OF.—Vascular tumors; angioma.

**DEFINITION.**—Under the general title of vascular tumors, only the blood-vessel tumors of *new* formation (neoplastic), originating essentially by proliferation of vascular walls or from a matrix of angioblasts, will be considered in this article. This definition excludes from this class of tumors all swellings caused by *dilatation* of pre-existing blood-vessels: Aneurisms and varicose veins.

**VARIETIES.**—Tumors originating from blood-vessels have been grouped according to the character of the affected tissue, the clinical peculiarities of the growths as to color, etc., or their anatomic and histologic peculiarities—the last the most scientific and satisfactory classification (Borrmann's classification).

The writer reviews 50 cases of blood cysts in the neck.

**Compression** of the tumefaction reduced it completely in the case of a babe of 4 months. Evacuation of blood never induced complete obliteration. In some cases 5 Gm. (1¼ drams) a day of a 1 to 5 **iodine solution**, injected into the cavity, was followed by cure, but this method is too dangerous, Woerner's patient dying suddenly after the injection. **Total enucleation** was performed in 23 of the cases.

It is advisable to ligate the afferent veins beforehand to minimize hemorrhage; likewise the efferent veins to prevent gas embolism. These ligatures need not be tied unless necessity arises. In cases with extensive adhesions, some have resected part of the cyst wall and painted what was left with phenol and alcohol, but total enucleation ensures a complete cure. Nasseti (Clinica Chirurgica, Oct. 31, 1917).

**1. Angiomata, or hemangiomata:** Large blood-filled spaces lined with

a single layer of endothelium, benign in character, the lesion probably growing as the result of an increase of the surrounding connective tissue and of a non-malignant proliferation of the endothelia.

(a) **Simple, or Capillary, Angioma.**—Synonyms: *Telangiectasis, angiotellectasia, angioma glomeruliforme, plexiforme; nævus vascularis or sanguineus; birthmark, mother's mark, Feuermal, Gefäßmal, tache de feu*. Vascular nevi have been designated according to their color, shape, and distribution: *Nævus vasculosus vinosus* ("port-wine mark"), *nævus araneus, nævus prominens, nævus vasculosus tuberosus, mulberry or strawberry nævus, venous nævus, pulsating nævus, nævus unius lateris* (Bärensprung), *nævus linearis* (Unna).

Superficial capillary angiomata are usually limited to the papillary layers of the corium, rarely extending beyond the subcutaneous cellular tissue. The growth consists of dilated capillaries and small veins, separated by a variable quantity of connective tissue. It is always present at birth, but may be so faint in color and small in size as to cause it to be overlooked until it enlarges.

Case of telangiectasis of the spinal cord in a man of 50. It was located between the 7th and 10th dorsal vertebræ. A laminectomy was done, but the group of varicose veins found not removed. Nevertheless, some benefit resulted. The case had been diagnosed as syphilis. C. H. Frazier and E. C. Russel (Arch. franco-belges de chir., Feb., 1925).

This type of angioma may be cutaneous or subcutaneous, the latter remaining concealed under the normal skin until this becomes stretched out and thinned, terminating in the cu-

taneous form or in a true cavernous angioma. In addition to its peripheral extension, the tumor may develop downward and inward, into the corium and connective tissue, leading to the clinical picture of elephantiasis telangiectatica.

*Clinical Manifestations.*—The condition manifests itself externally by one or more sharply outlined reddened spots of flattened elevations of variable size, with circular or ragged contours, and of the same consistence as the healthy parts. Superficial angiomas are frequently multiple, larger spots being surrounded by spattering of smaller ones. The color of the affected portions varies from pink to purplish, depending upon the superficial or deep situation of the vessels. The discoloration is generally not sharply outlined from the healthy tissue. The seat of predilection is in the skin and subcutaneous tissue, also the adjacent mucous membranes (lips, lids, cheeks). Simple hemangioma is occasionally found in adipose tissue, especially of the orbit; in the muscles, the mamma, in the bone, brain, and spinal cord. With the exception of the pleura, testes, cartilaginous tissue, and certain parts of the nervous system, there is said to be no portion of the human body in which these vascular tumors have not been observed (Mauclaire and de Bovis). Although no portion of the body is entirely exempt, fully two-thirds of all these angiomas affect the skin of the face. According to Lexer, based upon the statistics of Trendelenburg, who collected 170 cases, the majority affects the cheeks and forehead, next in order the lips, the nose, the surroundings of the ear, and the eyelids. Weinlechner places

71 per cent. of all cases at the head, especially the face.

(b) **Cavernous Angioma.**—Synonyms: *Cavernoma*, *nævus prominens*. Larger than a capillary angioma; it is characterized by irregular blood-spaces lined with endothelium and formed by a connective-tissue stroma containing elastic fibers, closely resembling the normal erectile tissues of the body, *e.g.*, penis, clitoris, etc. The blood-spaces freely communi-



Cavernous angioma of hand. Palmar aspect. (Author's collection.)

cate with each other and are nourished by their own arteries, which empty their blood into dilated veins. The growth may appear as a diffused, ill-defined mass, but more often as a circumscribed tumor, which may have a distinct capsule. The consistence or density of the growth varies with the size of the blood-spaces, the amount of stroma, and the possible formation of angioliths, or blood calculi. The blood contained within these spaces is the cause of the purple or dark-red color of the growth. Sometimes there is a more extensive purple discolora-

tion and thickening of the skin, with marked development of cavernous tissue in the subcutaneous or intermuscular connective tissue, which may lead to the formation of large tumors, with great deformity of the affected parts. A cavernous angioma may be sharply differentiated from the surrounding tissue or it may merge gradually into it. Increase in size takes place partly by expansion and partly by infiltration, new blood-spaces forming in the fibrous septa



Cavernous angioma of face of congenital nevoid origin. Removal by extirpation. (Author's collection.)

and at the periphery. The development may be steadily and slowly progressive or there may be periodical exacerbations. When a cavernoma has a distinct capsule, its growth may become spontaneously and permanently arrested. In other cases the retrogressive changes remain limited to individual segments of the tumor. Seen on cross-section, the structure of cavernous angioma reproduces the erectile tissue of the penis, whitish septa of variable thickness bounding the communicating blood-spaces. These septa are formed of fibrous tissue and the remnants of

the tissue in which the cavernoma has developed (Billroth).

*Clinical Manifestations.*—Cavernous angiomata may appear in the form of small purple spots or of smooth or roughened purplish warts which project above the surface. Certain extreme cases of monstrous cavernomata are on record involving large areas of skin, the entire head, face, and extremities, but these possess less interest for the surgeon than for the pathologist. With special reference to their localization, cavernous angiomata most frequently affect the skin and the subcutaneous cellular tissue (cheeks, eyelids, lips, cranial coverings). When situated in the face they are apt to give rise to distressing deformities, and in the cranial coverings, to very severe pain, on account of the involvement of nerves (trigeminal branches).

Series of 23 cases of angiomata in babies, some having more than one. Of 29 locations affected, 25 were about the head, mostly on the face. Fourteen showed a slight lesion at birth, others 2 to 4 weeks after birth. Immediate treatment is indicated. Twenty cases were treated with radium, under adequate screening. G. D. Culver (Arch. of Derm. and Syph., Dec., 1923).

(c) **Plexiform Angioma.**—Synonyms: *Cirroid aneurism*, *angioma arteriale racemosum* (Virchow), or *serpentinum*; *aneurisma per anastomosis seu anastomosen*; *tumeur erectile, cirroide*; *vascular pulsating tumor*; *arteriectasia diffusa cirroides*, *varix aneurismaticus congenitus*, *phlebarteriectasis*, *tumor vasculosus arterialis*.

Plexiform angiomata are more or less distinctly outlined tumors, developed from newly formed blood-vessels and occurring in definite arterial regions; usually (88 per cent.) originat-

ing from a congenital telangiectasis (nevi), more rarely in connection with traumatism (12 per cent., Fischer). The growth is made up of either arteries or veins, or of both arteries and veins in equal proportions. The arteries of the scalp and face are those most commonly affected, more rarely those of the extremities, the upper predominating (fingers, hand, and forearm). The

in the veins in the terminal stages. Plexiform angioma is most commonly derived from simple congenital angioma, and presumably develops upon congenital faulty development of a definite arterial area (Lexer). The trunks and branches at the seat of the process are involved up to the finest capillaries and ramifications, and the vessels of a lower grade become trans-



Cirsoid aneurism or aneurism by anastomosis. (Author's collection.)

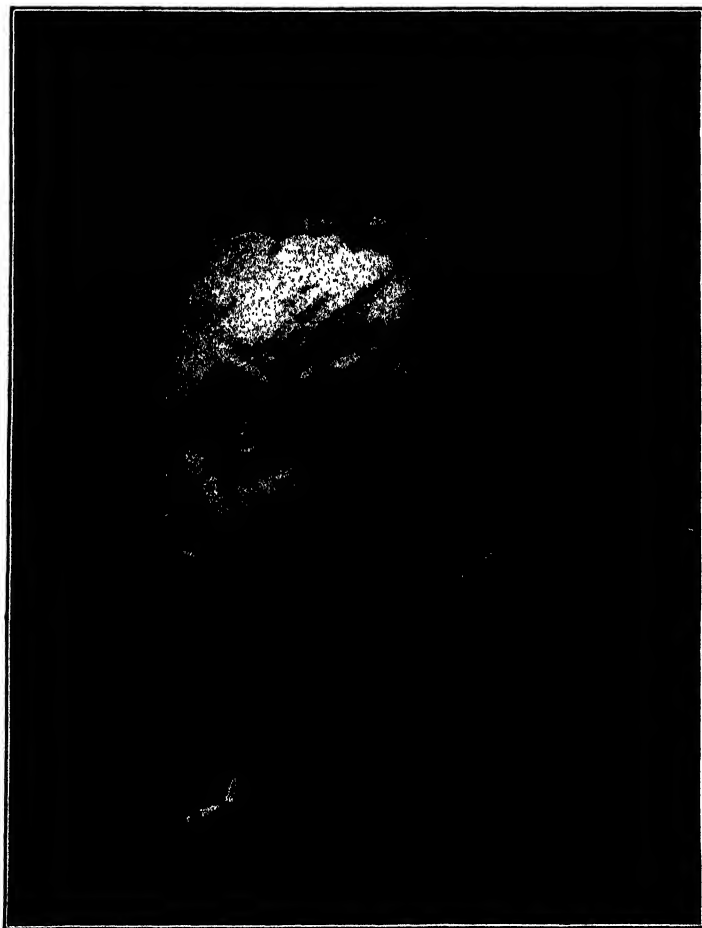
growth may develop in pre-existing blood-vessels, due to an excessive formation of angioblasts in the vascular wall (Senn). The tortuous vessels present a parallel arrangement. New blood-vessels form as the tumor increases in size, which continue to communicate with the lumen of the altered vessel. The growing tumor involves the small and middle-sized arterial branches of the immediate surroundings, finally affecting the large trunks, which become dilated, lengthened, and twisted. Similar changes are observed

in the veins in the terminal stages. The condition, which has nothing in common with aneurism, represents a pathologic vascular proliferation, probably on a congenital basis, involving an entire arterial area, and consisting in the new formation of a network of hypertrophied and dilated arteries (Ziegler). The true neoplastic character of this form of angioma was first pointed out by Virchow.

*Clinical Characterizations.*—The skin covering a plexiform angioma is thinned out, discolored, and locally adherent,

forming a flattened tumor which gradually passes into the surroundings. It conveys to the touch the peculiar sensation of squirming fish bait, due to slipping away of individual vascular cords under the examining finger. Pulsation

in the head, on account of the large number of anastomoses. The atrophic skin covering may break down leaving obstinate ulcers with a tendency to hemorrhage and infection. Persistent, profuse, and often uncontrollable



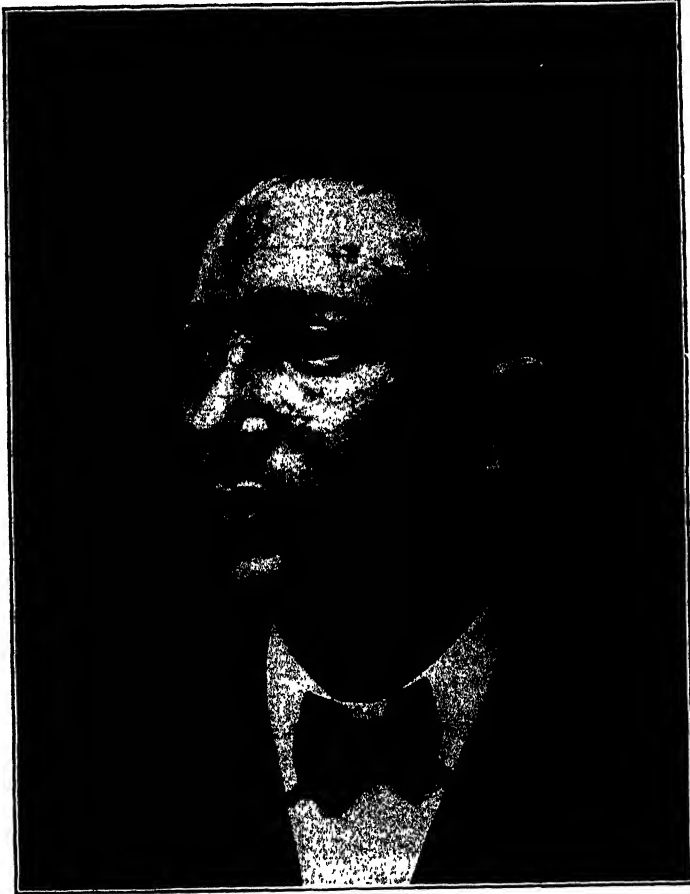
Angioma racemosum. Side view. (Carl Beck.)  
(Annals of Surgery.)

and bruit are usually well marked, the skin over the tumor vibrating synchronously with the heart-beat. Direct pressure upon the principal arteries causes a complete or partial evacuation of the tumor, with subsidence of the above phenomena when the growth is situated at the extremities; not so

hemorrhages lead to posthemorrhagic anemia and to death. Common clinical symptoms of plexiform angioma of the head are vertigo, pain, and functional disturbances due to infiltration of nerve cords and muscles. In general terms the clinical phenomena of plexiform angioma and arteriovenous aneurism

are identical because the lesions of the two conditions are analogous (arteriovenous anastomoses with arterialization and hypertrophy of veins). Another resemblance is a nutritional disturbance sometimes shown by an increase in size

*l'Acad. de Méd.*, 1833, t. iii, H. 101; Burci: *Contributo all studio dell'aneurisma circoide*, *La Clinica Moderna*, January 3, 1906; Simmonds: *Ueber Angiomaracemosum und Serpentinum des Gehirns*, *Virchow's Arch.*, vol. clxxx, 1905; Fischer, F.: *Das arterielle*



Lines of ligation and incision. Four weeks after extirpation. (Oarl Beck.)  
(*Annals of Surgery.*)

of the bones, the muscles, the skin and its appendages; in fact, no substantial difference between plexiform angioma and arteriovenous aneurism is recognized by some observers (Burci). The pathogeny, however, is essentially different.

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Virchow: *Die krankhaften Geschwülste*, vol. iii, 423; Petit, T. L.: *Oeuvres chirurg.*, 1740, t. i, Fig. 248; Bell, T.: *The Principles of Surgery*, London, 1826, vol. iii; Pelletan: *Clinique Chirurg.*, 1810, Fig. 59; Dupuytren: *Leçons orales*, Paris, 1839, t. iii, Fig. 43.

**GENERAL HISTOLOGY.**—The structure of angioma varies from independent vessels with distinct walls (simple angioma) to a true areolar tissue resembling erectile organs (cavernous angioma, *tumeur erectile* of Broca). Simple vascular tumors contain an abnormal number of large and otherwise altered capillaries and veins within a tissue normally belonging to the body. The new blood-vessels which constitute the growth are formed by budding of atypical angioblasts, the progressive tissue proliferation resulting in the formation of the tumor tissue proper. The endothelial lining of the vascular spaces—capillary, venous, or arterial—is the product of the angioblasts, a modified form of fibroblasts. Active proliferation follows in the other elements of the vascular wall, terminating in the formation of the outer and middle coats of the new vessels from connective-tissue and muscular constituents of the pre-existing vessels. While the constantly forming new blood-spaces establish communications with the older vascular spaces, the tumor as a whole remains sharply circumscribed from the surrounding tissue. The vascular walls contain flattened or cuboid endothelial cells and connective tissue in a circular arrangement. Growth takes place by the extension of vascular buds into their surroundings, the adjacent tissue becoming completely infiltrated by the constant new formation and dilatation of capillaries. While this manner of growth has the infiltrating character of malignant neoplasms, de-

stroying the affected parts inclusive of bone, metastasis of angiomatous tumors has never been observed, and there is no tendency to recurrence after complete removal. The increase in size is alternately slow and rapid, sometimes interrupted by long intervals, or permanently arrested at some stage of growth. The principal seat of angiomata is in the papillary layers of the corium, but the entire corium as well as the hypoderm may be involved. There often is a more or less well-marked increase of connective tissue in the surrounding of the vessels, and in extreme cases no tissue remains exempt. All vascular growths communicate very freely with blood-vessels (Senn).

In some capillary angiomata the process is chiefly or wholly limited to the arterial capillaries, while in others the veins are especially involved (venous nevi; venous angiomata). The more the external capillary budding predominates, the more rapidly does the angioma extend in all directions; the more the interstitial endothelial proliferation, the more does the tumor tend to encapsulation and remain stationary (Unna). Telangiectatic tumors, as a rule, are not sharply circumscribed, but have a tendency to extend in various directions into the surroundings. Their vessels are more independent than the blood-spaces of cavernomata, which are held together without a true wall by the intervacular connective tissue, an essential part of the entire structure. Cavernous angiomata of the skin are made up of an area of enlarged blood-vessels which is sharply differentiated from the subepithelial tissue on the one hand and the deeper corium on the other. The arterial wall of these vessels consists only of endothelium directly applied

to the surrounding connective tissue, which shows a circular arrangement. This tissue is more or less strongly developed and not of the same width throughout, so that small groups of vascular segments may be divided by dense connective-tissue septa from other similar groups. In this manner the angioma is divided into individual lobes. When development is active, the vessels are small as compared with the width of the intervening connective-tissue septa, but subsequently this disparity is reversed. The connective-tissue substance itself is usually poor in cells, but numerous nuclei are occasionally met with. It passes over into the corium, surrounding the neoplasm in such a way that there is no actual and distinct boundary. The plexus of blood-filled channels gives the impression, however, of an independent and separate structure. There is no transition to the vessels of the neighborhood and no indication of a transformation of the lumina into capillaries or *vice versa*.

Case of a child aged 2 years with numerous hemangiomata tuberosa in the skin, said to have appeared during an attack of bronchitis. The tumors were nodular, slightly raised, from pinhead to pea size, and yellow-brown or livid-red. Histologically, they showed an exceedingly cellular connective tissue with numerous capillaries, each usually surrounded by several layers of endothelioid cells. There were no cavernous formations nor deep-growing tubular processes. O. Marx (Derm. Woch., Jan. 26, 1924).

**Histologic Affinities, Combinations with Other Growths, General Complications.**—Upon this basis of histologic relationship, combinations with other tumor tissue have been observed to occur, especially as angiolipomata and angiofibromata. These tumors consist anatomically of a basis of adi-

pose tissue, connective tissue, or muscle tissue, and may be highly vascularized by extensive canalization with blood-vessels. Cystic transformation is also met with. A fatty change takes place by infiltration of the angioma with adipose tissue. Certain congenital lipomata are probably in reality degenerated vascular tumors. It must be admitted, on the other hand, that fat-tissue furnishes a favorable soil for the evolution of the angiomatous process. A simple hemangioma is not infrequently transformed into a cavernous angioma, especially in adipose tissue, the dilated capillaries forming a great cavernous system, with gradual atrophy and rupture of the interstitial tissue. Fibrous transformation is probably, as a rule, the result of interstitial inflammation between the capillaries, either due to external irritation or altered nutritional conditions of the connective-tissue elements. Spontaneous cure may occur as the result of contraction of scar-tissue and obliteration of the vessels. Cystic changes are not uncommon and have been accounted for by the separation of a vascular segment, which subsequently becomes dilated. It is less probable that cysts formed outside the vessels enter into communication with the vessels after giving way of the cyst-wall. The surface of these cysts is lined with endothelium, and their contents consist either of a hemorrhagic or a serous fluid.

Transition forms of hemangioendotheliomata occur as the result of transformation of vessels into narrow blood-filled tubes with thickened walls or into solid endothelial cords (collapsed vessels). There is a close relationship between angioma and en-

dothelioma, the cellular elements of the former having the characteristic shape and arrangement of the parent soil (Senn). A cavernous angioma occasionally undergoes a parietal hypertrophy, the flattened endothelia becoming transformed into cuboid and cylindric cells (hypertrophic cavernous angioma or vascular endothelioma). In other cases, nests of large cells take the place of the blood through marked development and increase of the endothelia (hemangioid endothelioma, Ziegler). Vascular tumors are subject to hyaline and colloid degeneration, and to calculus formation resembling the phleboliths of varicose veins. Septic thrombophlebitis may occur as a complication of inflammation induced for curative purposes. Obliteration of all the blood-vessels may take place through extensive thrombosis, or the further growth of the angioma may be arrested by calcification of the stroma and of the vascular walls. Angioma of the superficial capillary type has been known to become transformed into a plexiform angioma or a sarcoma. Malignant neoplasms starting from dilated veins and formed from them by the development of new vessels are of very exceptional occurrence. The telangiectatic transformation of a malignant neoplasm must not be mistaken for cancerous change of a vascular growth. On the other hand, cavernous tissue not infrequently develops within the various tumors of the connective-tissue group.

Devic and Tolot, in reporting a carefully studied case of angiosarcoma of the membranes of the cord with coincident multiple angiomas of the spleen, left Eustachian tube, the mediastinum, and celluloadipose

capsule of the left kidney, discuss the question of the possible transformation or malignant degeneration of angiomas. Their researches in the literature would seem to show that apart from this observation (and this case is doubtful) no cases have been reported which demonstrate conclusively that an angioma can be evolved into a carcinoma, though a carcinoma may become telangiectatic. An epithelioma or carcinoma of the skin or elsewhere may be grafted into a nevus and ultimately blend with it, but the angiomatous tissue cannot be *transformed* into an epithelial neoplasm. The authors agree with Cornil and Ranvier that an angioma may become sarcomatous, or *vice versa*, as these are tissues of the same derivation.

The angioblastic sarcomas or hemangio-endotheliomas are less malignant than the connective-tissue sarcomas. They often recur, but rarely metastasize. Klinge (Zeit. f. Chir., Nov., 1923).

**ETIOLOGY AND PATHOGENESIS.**—It is generally agreed that the vast majority of these growths are congenital and, with the exception of the traumatic angiomas developing in cicatrices and after injuries, the senile and other acquired types owe their origin to developmental disorders or defects in prenatal life. The vast majority appear at birth or shortly after. Of 558 cases, 500 appear in children under 12 months of age; 50, between 2 and 3 years, and only 8 between 4 and 15 years (Parker). Of 142 children treated in the Zurich clinic the congenital existence of angiomas was demonstrated in 82, and their appearance, a few days or weeks after birth, in 60 (Kraemer). *Sex.*—Statistics agree in giving the female sex a preponderating influence

(62 per cent. girls, Porta and Lebert); 365 girls to 172 boys (Parker); twice as many girls as boys in Gessler's collection of 1265 cases, and 71.4 per cent. girls in the Zurich clinic (Kraemer). For esthetic reasons it is probable that girls are often brought to the surgeon for treatment when the same condition is neglected in boys. It is statistically proved (Kraemer) that girls are brought to treatment at an earlier age than boys. A large number of the blemishes disappear after birth. Depaul claimed, with great authority, that fully one-third of the children born at the Clinique Obstetricale of the Faculté, Paris, showed nevi, which disappeared, in many, a few days or weeks after birth. *Heredit*y undoubtedly plays an important part in the transmission of these defects, though to a much less extent than was at one time attributed to this influence (16 per cent., Kraemer).

In describing 3 cases the writer refers to other families occurring in the literature, stating that his series is the first to be recorded in Scandinavian medical literature. He considers the hereditary disposition towards the development of multiple telangiectases to be of a degenerative nature, in which toxic factors, especially alcohol, may play an important part. A description of the microscopical appearance of the lesions is given. E. Gjessing (*Hospitalstidende*, Nov. 10-17, 1915).

Three cases of this remarkable condition occurring in 3 generations of 1 family. The principal symptoms were epistaxis and occasional bleeding from the lips, gums or even from the skin. The bleeding always took place from small nevi. These nevi were usually round red spots, about the size of a pinhead, though occasionally the familiar "spider" forms were met with. They were situated chiefly on the cheeks, the skin of the

nose, ears and on the mucous membrane of the lips, nasal septum, hard palate, tongue and pharynx. A few spots were also observed on the hands and about the shoulders. Hutchinson and Oliver (*Quart. Jour. of Med.*, Jan., 1916).

The writer observed hereditary hemorrhagic telangiectasia in 2 families, a condition made a clinical entity by Rendu. It attacks both sexes equally, and is transmitted alike by both. Twenty families have been recorded. In one of the author's cases the syndrome was traced through 5 generations. W. Steiner (*Amer. Climat. and Clin. Soc.; Med. Rec.*, Oct. 7, 1916).

The *pathogenic theories* which have been suggested to account for the origin of these growths are innumerable and, even now, their mode of origin in the skin and tissues is problematic and highly debatable. Their great frequency in the most conspicuous parts of the body (face and head), and their disfiguring effect upon the countenance, has invested them with a special interest to the masses from the remotest antiquity to the present time. At first attributed to supernatural influences,—the expression of divine anger,—popular tradition, confirmed by professional opinion, gradually transferred their causation from divine wrath to the influence of emotional impressions of the mother on the unborn child. "Maternal impression" expresses a conviction, which is preserved in the name "mother's mark," which clings to the lay mind with unshakable tenacity and, to some extent, in a disguised form, in that of many contemporary medical observers. Discarding the antiquated theories which have had their day and are now buried with past generations, we will briefly mention a few which are acceptable to modern teaching and pathology.

[I. *Localized disorders in the nutrition of pre-existing vessels leading to progressive hyperplasia* (Virchow) or regression to the embryonal type with neovascular formation. Virchow pointed out the existence of both an active and a passive process in the evolution of these tumors and showed that cavernous angioma originated through the dilatation of pre-existing vessels, both old and new, the vascular walls being thinned out by dilatation and gradually undergoing absorption. According to Journiac, the vessel walls become gradually softened and united with each other as the result of embryonic proliferation in the pre-existing vascular endothelium. This mode of formation appears most probable in the acquired angiomas—especially the cavernous and cirroid—in which traumatism and infection are the exciting causes ("vascularitis," Coulon), as illustrated by Reverdin's, Klippel and Trenau-nay's, and other cases.

II. *Independent neovascular formation of migratory embryonal buds detached from germinal areas and leading an independent existence.* Ribbert, with whose name this application of Cohnheim's theory is especially associated, after demonstrating (by injection) the circulatory independence of the angiomas and their relative isolation from the surrounding vessels, supports this view by the frequency with which nevi appear on the face and head (cheeks, lips, eyelids, and root of nose), where the branchial clefts existed, thus favoring the sequestration of highly vascular germinal tissue. In a modified way this is an application of Virchow's explanation of the fissural angiomas, which bear the same relation to the branchial clefts. "A very slight irritative condition at the borders of the fissures, which are very abundantly supplied with vessels, is sufficient to induce a great vascular development which might possibly be recognized as a nevus, but which remains latent and only later becomes manifest" (Virchow). Thus, according to this theory (recently revived by Lamy), there are, "angiomas of the frontal germinal area," of the "superior maxillary area," of the "inferior maxillary area," and those of the "second branchial arch." This interpretation according to germinal areas is confirmed to some extent by the analogy which angiomas present with other congenital malformations in the same regions (inter-

maxillary clefts, branchial cysts, fistulæ, and tumors).

III. *Influence of physical or mechanical surface pressure on the fetus*—"intra-uterine pressure theory of Unna." This theory strives to account for the fact that nevi appear usually in regions which are most likely to suffer from pressure during prenatal existence. For example, an extraordinary proportion of individuals, according to Unna, have nevi in the neighborhood of the occipital fontanelle, hidden by the hair in adults (35 per cent. of newborn infants, though only traces remain in adult life—10 to 20 per cent.—Politzer). Pressure would cause a localized compression anemia, followed by a paralytic hyperemia and ultimately a nevus formation. The vasomotor phase of this theory gives it some affinities to the "vascular theory," expounded with considerable ingenuity by Trelat and Monod (1869), and supported by the great authority of Barwell. These authors argued for a localized vasomotor paralysis in embryonic life from central lesions followed by hypertrophy of the vessels and the surrounding tissues.

IV. Of all the theories propounded, that which at present appears the most attractive is the "*neural theory*," originally foreshadowed by Royer (1835), Arndt (1839), and more clearly stated by Bärensprung, in 1863, when he reported 4 cases of *nevus unius lateralis*, and called attention to the topographic distribution of the nevi in segmentally innervated cutaneous areas. He attributed this systematic distribution to a prenatal injury or disease of the spinal ganglia, basing his belief upon: (1) The affection is unilateral and is accurately bounded by the median line; (2) the distribution corresponds to the peripheral expansion of one or more spinal nerves; (3) the cutaneous changes consist in hypertrophy of the elements in which terminate the peripheral nerves, namely, the cutaneous papillæ—glands, hair-follicles, etc., not participating in the lesion. He also called attention to the similarity of zona to nevus in its paraneural skin distribution. While Bärensprung's observations were very favorably received, other observers (Phillipson, Petersen, Galewki) reported other cases in which the nevi appear to be related to Voigt's lines, which define the zone of separation between

the functional spheres of two adjacent cutaneous nerves. In this way they attached the appearance of the nevus to symmetric *vascular*, rather than peripheral, nerve lines. While a number of cases seem to conform to these lines of demarcation, this disposition along Voigt's lines is far from constant. Other observers (Pitres and Vaillard) also attempted to modify the "neural theory" by associating the nevus formation with *peripheral trophic disturbances in the cutaneous nerves*. Subsequently, further inquiry into the neural distribution of zona (Brissaud) led to the expansion of the ganglionic theory of Bärensprung, into the spinal *neuron* or "*metameric theory*," by which the prenatal lesion was transferred from the spinal root ganglia to the cord itself. The distribution of the nevi in definite dermatomeres, corresponding to definite spinal segments or neuromeres, a view ably advocated by Lelong, has met some of the objections to Bärensprung's original views and gained for the neural theory many adherents.

In an interesting case reported with great care by Heide (Copenhagen), a large, diffuse cavernous angioma of the left lower extremity associated with extensive varices and pachydermia (elephantiasis teleangiectodes), he remarked that the metameric distribution of these lesions had been observed in connection with small groups of cutaneous nevi only, or in a few instances of large telangiectases in the skin, but not in extensive cavernomata. However, the skin areas affected in Heide's patient were found to conform exactly to the cutaneous distribution of the branches of the sacral plexus, while those innervated by the lumbar plexus remained intact.

Dr. Harvey Cushing, in a very thoughtful contribution, also reports 3 cases of nevi occurring in the distribution of the trigeminus, which he found associated with a similar condition of vascularity in the dura—also supplied by the same nerve. His observations support Bärensprung's ganglionic theory, which presupposes a prenatal lesion of the Gasserian ganglion caused by infection or injury.—R. MATAS.]

While the topographic distribution of some nevi and other surface angiomas is satisfactorily explained by the neurometameric theory, the mechan-

ism by which the nerve lesions cause the vascular ectasis and the correlated histologic disturbances still remains unaccounted for.

Klippel and Trenaunay, in a very praiseworthy review of the subject, concluded that the rôle of the nervous system is secondary. It merely prepares the soil for infection by diminishing the local resistance, and thus prepares the way for the localization of the infectious or toxic agents in the blood-vessels, where they act as the exciting cause of the abnormal growths. In this they accept the views of Coulon in accounting for the acquired traumatic angiomas of post-natal life (see cases reported by Reverdin, Mauclaire and De Bovis, Duplay and Cazin, and others) by infection in the blood-vessels themselves.

Again, in confirmation of the influence of the nervous system in the genesis of vascular growths the remarkable class of tumors grouped by Klippel and Trenaunay, under the title of "*ostcohyertrophic varicose nevus of the extremities*" (previously described in the literature as "partial unilateral hypertrophy of the extremities" and under other titles), is well worthy of attention. This complex form of angiomatous disease is characterized by (1) a nevus involving the entire lower extremity, having a metameric distribution; (2) premature varicose veins limited to the diseased side exclusively and dating from childhood, if not from birth; (3) hypertrophy affecting all tissues of the diseased side, but especially the skeleton, which is increased in all dimensions—in length, width, and thickness. The disease is associated with certain other local, trophic, and nervous dis-

turbances, which may, however, be regarded as accessory. The entire triad of symptoms and manifestations are attributed to a common origin, probably a central metameric or trophic lesion of the cord, associated with infection localized in the peripheral vessels of the affected extremity and occurring as a prenatal disease.

**DISTRIBUTION.**—(a) **Skin and Deep Connective Tissue.**—Capillary or surface angiomas, as the name implies, are situated in the skin, preferably on the face and mouth, but sometimes extend over an entire side of the face or even one-half of the body. Cavernous and plexiform angiomas occupy the deep connective tissue, which is the primary seat of the growth in a number of cases, or this may be involved by extension from the skin. In the former case, the skin covering of the tumor generally presents a healthy appearance, unless the skin becomes atrophic and ulcerated as the result of pressure, malnutrition, or traumatism. In rare cases, simple angiomas are found in adipose tissue, especially in the orbit.

(b) **Skin and Mucous Surfaces.**—Angiomas of the mucosæ are of rare occurrence, and very few cases are on record where the growth presented in other mucous membranes than those of the tongue and the rectum. Involvement of the mucosa by extension from the skin is more common. Next to, in, and under the skin, simple angiomas are found with especial frequency in the adjacent mucous membranes (lips, lids, cheeks). The cause seems to be a dilatation of the capillary vessels in the delicate network of the subepithelial layer.

(c) **Muscular System.**—Primary

angiomas of the muscles are growths which develop from the vascular plexus of a voluntary muscle, or in the perimysium between the muscle-fibers. They may be either simple (rare) or cavernous in type. The arrangement of the vessels in these cavernous angiomas of muscles is extremely variable. Although veins are found more rarely than arteries, they are not entirely absent. When present in considerable numbers, the lumen of the vessels is much enlarged, and in certain cases this venous dilatation seems to have constituted the first phase of the cavity. The capillaries are the most important element in this connection, giving rise to simple angioma not only, but resulting by marked dilatation and fusion in the blood-spaces of cavernous angiomas. With special reference to the pathogenesis, the origin of these growths has been referred to a congenital malformation of the vessels, which does not manifest itself until an advanced age of the individual (Sutter). The existence of a faulty congenital disposition of a circumscribed tissue area has been responsible (Ribbert, Riethus). Increase of the interstitial connective tissue and the adipose tissue in the muscle has been regarded as the primary change, followed by the development of capillary vessels and terminating in atrophy of the connective tissue, with ultimate production of a cavernous space (Pupovac). A history of traumatism is given in too many cases to be regarded as merely accidental. The growth is rarely larger than an orange, and the increase in size is very gradual. The surface of these tumors is lobulated, and they vary as to size and consist-

ency, being usually doughy to the touch and sometimes pulsating.

They may present as mixed tumors, with lymphangiomata or lipomata (fibrolipangioma). A cavernous tumor of the semimembranosus surrounded by a lipomatous mass was reported by Keller, who found 22 corresponding cases in the literature (compiled by Alessandri). A case of fibromyangioma characterized by marked proliferation of non-striated muscle in a peripheral muscle was reported by Honsell. An extremely rare, perhaps unique, case of cavernous angioma situated in the intermuscular adipose tissue, between the serratus anterior and the latissimus dorsi, was recently observed by Kuttner. This tumor could not be classified as a true muscular angioma, on account of the intact condition of the skin, the subcutaneous cellular tissue, and the muscle, and also the absence of any connection of the tumor with the deeper layers.

While primary angiomata of voluntary muscle are relatively rare, it is not at all uncommon for a cutaneous angioma to extend to the subjacent tissues, sometimes involving the muscles to a very considerable extent. The character of muscular angiomata appears to be benign in the majority of cases, but diffuse infiltrating growths always imply a potential malignancy. The rate of growth is very slow, sometimes extending over fifteen to twenty years. There may be no other than mechanical symptoms, while certain cases are characterized by severe pain, due to compression of large nerves by the growth, especially when this is situated at the extremities. The symptoms and diagnosis of these

growths will be referred to again under general diagnosis of angiomata. No other than surgical treatment enters into consideration, and, on account of the usually diffuse distribution of the growths in the muscle, operative interference, as a rule, will have to consist in extirpation of the entire affected muscle or muscle segment.

Muscle angiomata are particularly painful, nerves being compressed and undergoing marked histologic changes owing to the invasive property of the tumors. Compressibility is also diagnostically useful. Exploratory puncture is the most reliable means of diagnosis. These tumors may become highly malignant. Of the author's 3 cases, one had an angioma of the musculature of the leg, extending to the bone, with contracture at the knee and pes equinus. The second angioma was in the scapular region and necessitated resection of the circumflex scapular artery and lower scapular angle; there were 3 recurrences. The third angioma developed in the right hypothenar region after trauma and was excised. F. Furnau (Arch. f. klin. Chir., Sept. 23, 1924).

(d) **Osseous System.**—Angiomata in bone (myelogenous angioma of Virchow) are of extremely infrequent occurrence. They are invariably produced by the formation of new blood-vessels from a matrix of angioblasts (Senn). The resemblance to osteosarcoma, a relatively very common affection, is so great as to render a positive *intravital* diagnosis impossible. Pulsation is sometimes present, due to the great vascularity of these growths, and has led to the erroneous diagnosis of bone-aneurism. The long bones are the seat of predilection of vascular tumors of the osseous system; usually near the articular or epiphyseal extremity of the bone,



where the vascular distribution is greatest. Of 23 cases of endothelioma and perithelioma collected by Howard and Crile, the humerus was affected 5 times; the ulna once; the iliac bones once; the femur 4 times; the head 3 times; the vertebral column twice; the sternum and ribs once; other bones 3 times.

Case of bone hypertrophy ascribed to a nevus. In a boy aged 7 the right leg was 1 inch longer than the left. The X-ray showed no structural difference. The right leg had a higher surface temperature and some brownish pigmentation with enlarged vessels about the knee. Increased vascularity about the growing ends of the femur and tibia is thought to have been responsible for the discrepancy. D. Patterson and W. G. Wyllie (Brit. Jour. Childr. Dis., Jan.-Mar., 1925).

**Parasynovial angioma** occurring in the knee-joint has been observed in 2 instances. In Martel's case the growth was not directly associated with the venous system, but connected with the arterial system, and constituted a plexiform angioma.

**TOPOGRAPHIC DISTRIBUTION.**—Of all forms of angioma, including the ordinary mother's mark, the usual localization is in the head and the least frequent in the limbs, as may be seen from the following table compiled by Ashhurst from Kraemer and Gessler:—

Head and Neck, 57 per cent. (Kraemer); 79 per cent. (Gessler).

Trunk, 28 per cent. (Kraemer); 11 per cent. (Gessler).

Extremities, 12.5 per cent. (Kraemer); 9 per cent. (Gessler).

**Head.**—*Intracranial* angiomata may belong to blood-cysts of bone developed from the nutrient vessels of the parietal bone. The cysts are

lined with endothelial cells, and their origin is referred to the angioblasts (Senn). *Meningeal* angiomata take their origin from the vessels of the pia mater, and have been found in the fourth ventricle and upon the surface of the middle lobe. Plexiform angioma of the brain is very rare. Simmonds collected 5 cases.

**Scalp.**—Simple angiomata of the soft cranial coverings, according to Heinecke, constitute 33 per cent. of the angiomata of the head. Cavernous angioma of the skull is apt to infiltrate the bone, communicating with the large blood channels through dilated capillaries and veins. Their intimate connection with nerves, especially trigeminal branches, may give rise to severe pain. Plexiform angioma preferably affects the arteries of the scalp and face.

**Forehead.**—This is the favorite seat of simple angioma, especially in the region of the glabella, at the inner end of the eyebrow, and over the fontanelles. Of 109 angiomatous tumors of the skull compiled by Heinecke, 38 were situated on the forehead. A typical case was reported by Berndt, the patient making a good recovery after extirpation of the tumor and ligation of the veins supplying it. Of 19 cases of arterial nevi collected by Vincent, 17 were situated exclusively in the head. They are not infrequently multiple, their number ranging approximately from 2 to 8, and may be the forerunners of plexiform angioma.

**Conjunctiva.**—Angiomata of the conjunctiva are very uncommon. Only 2 cases were observed in the course of twenty-eight years in an institution having an unusual polyclinic material of 8000 to 9000 patients

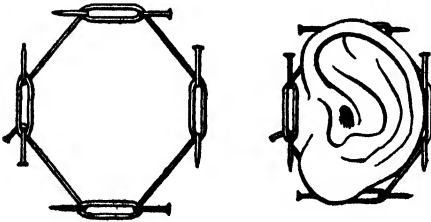
(Fehr). According to Virchow, angiomas of the conjunctiva represent either an extension of palpebral tumors, or they may develop primarily in the conjunctiva. The latter form is especially rare and hardly ever progresses beyond the nevus stage. In the majority of cases these growths are congenital or develop within the first few years of life (Saemisch). Their favorite seat is the internal commissure, especially the semilunar fold. They may remain latent during years and then gradually increase in volume, giving rise to disturbances, by increasing the tension of the conjunctival sac, until they finally protrude from the orbit. As in all angiomatous tumors, the diagnosis is based upon the color, form, consistency, enlargement, and manner of growth. Cavernous angiomas must be differentiated from highly vascularized lipomata and fibromata, which may simulate cavernous growths through excessive development of their blood-vessels. Of 17 cases of primary angioma of the conjunctiva observed by Fehr, 12 were of the cavernous type and 5 were telangiectatic. The growth in all these cases was very slow and superficial, these tumors being relatively benign. There was neither metastasis nor recurrence after radical operation, consisting in ligation of the tumor followed by excision.

*Eye.*—The bulb is endangered by progression to the orbit by angiomata of the eyelids, which may be involved primarily or by extension of the growth from the temporal and nasofrontal region. Cavernous angiomas sometimes originate in the orbit, and are either encapsulated or diffuse, resulting in displacement of the bulb.

The most important signs of cavernous orbital angioma are absence of pain, very slow growth, preserved motility of the eye, elastic consistency and compressibility of the tumor, and especially a tendency to swell under the influence of venous stasis. Pulsating exophthalmos, a pulsating tumor at the inner angle of the orbit with protrusion of the eyeball, has been observed as the result of distention of the dilated branches of the ophthalmic artery by a plexiform angioma. Angiomas of the choroid are rare. Six cases were compiled from the literature by Bossaline and Hallauer. Simple angioma is exceptionally met with in the adipose tissue of the orbit. Deep-seated angiomas of the orbit originate beneath the orbital aponeurosis in the celluloadipose tissue which surrounds the eyeball. They are, as a rule, arterial, pulsating, and infiltrating in character. Since the resistance of the bony orbital walls prevents their extension in all directions, they progress toward the front, either pushing the eyeball before them or passing above and, more rarely, below it. The eyelid is invariably raised up at an early stage of the growth. These orbital angiomas may acquire considerable size, stretching and thinning the bony walls and extending into the cranial cavity.

*Upper Air Passages.*—Vascular tumors are of relatively rare occurrence in this locality (Cobb, Kyle). With special reference to the nose, the frequency of these growths is not universally agreed upon. Jonathan Wright does not consider them to be as rare as commonly represented, mentioning about 30 cases from

American and German sources. In a total of 264 cases compiled by Schimmelfennig, 113 were located in the nose and 151 in the mouth and pharynx. According to Kyle, these growths are more often found on the nasal septum than on the turbinates. A large number of so-called tumors of the nose are bleeding polypi of the nasal septum. Mucous polypi and growths of the posterior portion of the turbinates may simulate vascular tumors, but these present a peculiar purplish or dark-red discoloration. Moreover, they are of spongy con-



These cuts are intended to give a schematic representation of the author's method of elastic constriction with the aid of pins, used as binding posts, to secure local anesthesia and hemostasis in all operations on the auricle.

This method was very successfully tried by the author in extirpating a gigantic cavernous angioma of the auricle.

sistency and are readily reduced in size by pressure.

Although they are almost exclusively congenital, vascular tumors of the upper air passages generally manifest themselves at an advanced period of life. Of 135 of these patients, 61 were men and 74 were women. In the treatment of these conditions the **galvanocautery** and the **hot snare** have proved most valuable.

Multiple telangiectases of the skin and mucosa of the nose and mouth have been reported by Kelly.

*Lips.*—At the lips, simple vascular tumors may simulate the picture of macrocheilia, the result of lymphangioma. Under these conditions, the upper lip, which is the one generally affected, hangs down over the chin in shape of an irregularly outlined purplish welt, the lower tip protruding like a proboscis. The swelling enlarges by changes of position (stooping) and on exertion (crying) or excitement. Virchow refers to the lower lip of Emperor Leopold of Austria, which hung down to the chin when the monarch's ire was aroused.

*Auricle.*—Angioma of the auricle, almost invariably of congenital origin, is seen with especial frequency in children. In the majority of cases, the growth involves the adjacent region of the cheek. It may be plexiform and telangiectatic, which is usually the case in the vicinity of the tragus, whereas in the remaining portions of the auricle the angioma is more apt to be cavernous. The condition acquires clinical importance on account of the tendency to hemorrhage. When the tumor is arterial in character, distressing ear noises are often complained of as the result of pulsation. Auricular angioma has been reported to follow puncture of the lobe of the ear for so-called ornamental purposes. In regard to the treatment it may be stated that multiple galvanopuncture, although frequently followed by recurrence, is preferable to excision, except in cases in which the entire cartilage is involved, when the pinna is to be amputated. (The author's method of controlling the circulation of the ear, either for partial resection or total amputation is here exhibited.)

In total amputations for malignant disease involving the auditory canal in which *total* excision is required, the method is not applicable for obvious reasons.

The root of the auricle is first infiltrated to the periosteum of the mastoid with beta-eucaine (0.2 of 1 per cent.) and adrenalin sol. (1:1000, 1 per cent.) in physiological salt solution (0.8 per cent.), an infiltrated zone which edematizes the root of the concha and surrounding tissues like a drop-sical collar. The solution is forced into the tissues with the author's infiltrating pump. Four pins are then inserted at equidistant points, and a thin rubber band is wound around them several times in the manner shown in the diagram. As the elastic thread is wound around the root of the pinna, the ear becomes markedly pedunculated, and its outline more contracted and circular, the lobule being thrown up toward the helix.

**Tongue.**—Both simple and cavernous angiomas have been observed to occur in the tongue. Gibson reports an interesting case, in which the growth began in childhood as a black spot on the tongue, and sixteen years later extended over the floor of the mouth, the parotid gland, and the hard and soft palate. The treatment was conservative, in view of the probability of recurrence. Senn successfully removed an extensive vascular tumor of the tongue by excision.

**Tonsils.**—Vascular growths, limited and confined to the tonsil, are rarely met with. Hartmann found only 2 recorded cases of angioma varicosa of the tonsil, to which he adds a personal observation. The growths are best removed very slowly with the cold snare, to avoid hemorrhage.

**Neck.**—The upper triangle of the neck sometimes is the seat of vascular growths. In a case observed by Elliott, a cavernous angioma of the neck developed five years after the removal of a small submaxillary angioma. The largest vascular space

was situated in the center of the tumor and was about the size of a lemon. Numerous other smaller cavities were distributed through the substance of the growth. A number of tumors situated at the point of bifurcation of the carotid were described by Paltauf, who suggested for these growths the designation endo- (peri-) thelioma intercaroticum. Valuable contributions to the subject of carotid tumor have been made by Keen, Funke, and Da Costa. Certain angiomas of the *parotid* region seem to involve the gland as well as the muscles and all the soft parts of the cheek.

**Breast.**—The mammary gland may be the seat of angioma, but this location is infrequent. Nine undoubted cases from the literature were collected by Malapert and Morichau-Beauchant, with the addition of a personal observation. The tumor is usually present at birth or develops within the first few months of life. It may be cutaneous, subcutaneous, or glandular, developing in the celluloadipose stroma of the gland. The glandular elements become atrophied as the angioma progressively enlarges. The growth is generally diffuse, but sometimes there is a distinct capsule (Bajardi's case). All angiomas of the breast have a tendency to progression. They slowly increase in size, the growth sometimes becoming accelerated as the result of traumatism. In other cases they remain stationary during variable periods. Complications are uncommon, but may occur in the shape of hemorrhage due to ulceration of the skin invaded by the angiomatous process. The treatment varies with the character of the tumor. Super-

ficial nevi may be treated in the ordinary manner, while subcutaneous growths are best treated by excision, unless the gland is involved, when entire removal of the breast is indicated for the prevention of recurrence.

Case of angioma of the mammary gland in a 22-year-old girl, which had

tuating and to contain a chocolate-brown fluid. Microscopic examination showed that the tumor was encapsulated and that the interior was composed largely of blood-vessels with some connective tissue around the larger-sized vessels. The tumor was a congenital hemangioma into which hemorrhage had occurred apparently because of some external



Multiple cavernomata of upper extremity. Ventral and dorsal aspects.  
(Courtesy of Dr. O. A. Porter, Boston.)

been gradually increasing in size since childhood. The last three years it had become painful. No injury had been received so far as the patient knew. The tumor was located in the upper outer portion and in the depths of the left mammary gland. Upon palpation it seemed to be either a fibroadenoma or a cyst. The patient desired operation because of the pain which the condition produced. During the operation it was found that the tumor, which was about the size of a walnut, could not be shelled out. After it was removed it was found to be soft and to a slight extent fluc-

influence. Although the operation had been done three years before the case was reported, there had been no recurrence at that time. Carl (Deut. Zeit. f. Chir., Bd. cxi, H. 1-3, 1912).

**Upper Extremities.**—Solitary angioma of the upper extremity is relatively frequent, whereas multiple vascular growths are uncommon, although instances have been reported by Virchow, Cruveilhier, Esmarch, Schuch, Gasne et Guillaïn, Abner Post, and others. Angioma of the entire upper extremity, extending from the

root of the neck to the finger-tips, in an adult male, was observed by Abbe. In the case reported by Gasne et Guillaïn (adult female) the vascular anomaly had existed from the time of birth, involving the right upper extremity and lateral thoracic region. In 12 cases of diffuse cavernous angioma of the extremities collected by Ashhurst, 10 involved the upper extremities.

*Hand.*—Congenital cavernomata are rare in the hand, but in many reports merely the upper extremity, in general, is mentioned as the seat of the growth. Next to the head, the hand is the seat of predilection of angioma, according to Kirmisson. Neither telangiectatic nor cavernous growths are uncommon at the hands and fingers. The majority of all digital tumors are simple or cavernous angioma (Koenig). In the remarkable case of cavernoma of the hand in a newborn child, recently reported by Franco, the right hand presented an irregular swelling nearly as large as the infant's head, involving the wrist, the carpus and metacarpus, and the first three fingers. In view of the monstrous development of the angioma and corresponding deformity, the treatment consisted in amputation of the forearm, which was readily tolerated and recovered from. The specimen was classified as a lipogenous cavernoma (Virchow), and its origin referred to the cellular adipose tissue. Angiokeratoma (telangiectatic and cornified nodules, Mibelli) is especially common in the hands (Rau).

**Lower Extremities.**—Only a small number of cases of plexiform angioma affecting the lower extremity are on record. Ten cases were compiled

from the literature by Froelich, 2 of which affected the gluteal region; 1 the patella; 3 the leg and foot; 3 the foot alone. The right and left sides were about equally represented. The reason for the rarity of the condition at the extremities as compared to the head lies in the fact that plexiform angioma frequently develops upon a telangiectatic base, which is most common in the head. Blood-pressure being much lower in the extremities than in the head, general hyperemia has a less marked effect. Moreover, the blood-supply to the extremities is physiologically less than to the head. The limb affected by plexiform angioma becomes swollen and markedly enlarged. It has been found to be from 2 to 3 cm. longer than on the normal side, and in 1 case the leg of the affected side was 5 cm. longer than the other. The treatment of these growths aims at the removal of the tumor as completely as possible and at the maintenance or restoration of function. Extirpation with or without previous ligature of the nutrient vessels of the tumor is the most rational and radical procedure, combining the greatest prospect of success with the smallest probability of recurrence. Partial excision is suitable for tumors too large to permit of complete removal. The risk involved in excision is hemorrhage, both primary and secondary.

A certain predilection for the lower extremities is shown by the very rare, diffuse, and extensive angiomatous formations known as *phlebogenous angioma* (Virchow). Presenting in the shape of multiple encapsulated tumors in the course of a large venous trunk, from whose vasa vasorum they seemed to originate,

these phlebogenous growths cannot be sharply differentiated from certain diffuse peripheral angiomas. Transition forms occur here as well as between any two other forms of angioma. A small independent group, not extensively represented in the literature, is characterized by the diffuse distribution and the tendency to invade the neighboring soft parts. The condition is well illustrated by a case recently observed by Heide, in which the left foot was affected, especially in the anterior portion, including the toes, the fibular side, and the sole of the foot.

The remarkable group of cases described under the title of Varicose Osteohypertrophic Nevus, by Klippel and Trenaunay (see Etiology and Pathogeny), are peculiar to the lower extremities, involving one or both limbs. The case reported by J. Adams, Chassaignac, Trelat, and Monod, Duzeu, Andry and Monan, Barwell, Duplay, and others collected by the authors mentioned, are remarkable illustrations of the localization in the lower extremities of this complex type of angioma.

**Splanchnic, or Visceral, Angiomata.**—*Liver.*—The most common seat of angiomata within the body is the liver, where they present in form of small foci which project slightly beyond the surface. They are of variable size, up to a few centimeters in diameter, and substitute the liver tissue. The growth is sharply differentiated from the surroundings by connective tissue. The origin is probably referable to a local disturbance of development, starting from the vessels of Glisson's capsule or from the interacinous capillaries. The process is characterized by an

abnormal vascular development and a simultaneous arrest of growth in the other tissue constituents. The increase in size of these tumors is very gradual and limited, and, as a rule, the liver-cells of the surroundings present no evidence of degeneration. The condition is most frequently discovered as accidental postmortem findings at the autopsy of aged individuals; but it is a remarkable fact that some of the largest specimens have been removed from children. The two largest hepatic angiomata operated upon occurred in adult women, 41 and 37 years of age, respectively (Rosenthal, Langer).

Keen, in his report of a case of angioma of the liver treated successfully by extraperitonealization and elastic ligature, reports 58 liver resections or operations for tumors from 1888 to 1897, compiled from the literature. Of these, 4 were angiomata, 1 cavernous, and 1 angiofibroma. These were nearly all treated by the elastic ligature of the pedicle outside of the abdominal cavity. It is probable that in future these and other tumors of the liver will become more amenable to direct intraperitoneal treatment, in view of the marked improvement in the technique of hepatic resection which has followed since the introduction of better methods of hemostasis by Kousnetzouff and Pensky, Cullen, Garré, and others (see section on Surgery of the Abdomen, Liver).

The lobulated structure of these growths in a general way resembles the structure of cutaneous cavernoma (Ribbert). The blood-spaces form various groups divided by septa into compartments of variable width which sometimes communicate with each

other. The width of the spaces and the thickness of the septa vary within very considerable limits. The inner wall is lined with endothelium, and smooth muscle-fibers are sometimes found in the wall of the vessel. A number of contradictory views have been expressed concerning the pathogenesis: "Failure of independent area to become incorporated into the liver in the typical manner" (Ribbert); "tissue malformation through faulty germinal predisposition" (Schmieden); "thickening of connective tissue with disappearance of vessels and subsequent atrophy of liver cells" (Rindfleisch and others). The stagnation theory, according to which proliferation of the vascular wall was caused secondarily by a local stagnation of the bile, has been practically discarded.

*Spleen.*—Altogether only about a dozen cases of cavernous tumors of the spleen are registered in the literature, including two observations upon animals. In the spleen the vascular spaces do not take the place of the missing parenchyma essential to the specific function of the organ; but the epithelial lining of the vascular spaces results in an increased physiologic function as compared to the normal splenic pulp. Important points in regard to the structure of the tumor are: the presence of vascular ducts in direct connection with the Malpighian corpuscles; the communication of the ducts with each other and with the cavities; the transition of ducts lined with high epithelium into venous capillaries lined with flattened endothelium; the formation of the parietal lining of the cavities by septa with a layer of flattened endothelium. A system of

canals in the spleen was described by Billroth and by Böhm, which essentially agrees with the characteristics of these cavernous vessels. Böhm says that the splenic pulp in man is composed of a canalicular system lined with typical epithelium, the canals being probably blood-capillaries of a peculiar structure. Billroth's capillary veins are assumed by Böhm to open into the Malpighian corpuscles. The various characteristic features are all reproduced in the cavernous ducts. According to Albrecht, the pathogenesis of cavernoma of the spleen is probably referable to a faulty predisposition of the local vascular apparatus (primary variation of Billroth's capillary veins).

*Alimentary Canal.*—Cavernous angiomas have been observed in this location, although with extreme rarity, in both children and adults. Approximately 20 cases are described in the literature. The growth usually occupies the stomach and esophagus or portions of the colon and small intestine. Fatal hemorrhage is apt to occur in those cases especially where the esophagus is the seat of the angioma; more particularly in children. In addition to the bowel, in a case described by Sommer, the bladder, the broad ligaments, the ovaries, and the retrovisceral cellular tissue of the abdomen participated in the growth. A case of multiple cavernous angiomas of the intestine was recently reported by McCallum. In another recent case, contributed by Bennecke, the cavernous phlebectases were distributed throughout the esophagus and the stomach, as well as the intestine. Metastasis has been observed in 1 case in the celiac ganglion.

The pathogenesis of these vascular



growths of the alimentary canal is not agreed upon, and four principal theories have been suggested: (1) Mechanical factors producing a rise of pressure in the portal vein (Orff). (2) Nervous influences injuring the power of resistance of the venous walls (not accepted). (3) Primary inflammatory changes in the venous walls (Lilie). (4) Primary malformation of the venous wall with imperfect development of the muscular and elastic constituents (Bennecke).

Cavernous hemangioma of the spleen of unusual size reported. A man of 42 had for 8 years had a feeling of weight in the gastric region. There was found a hard mass moving with respiration, with the liver displaced to the right, and increase of dullness by almost 2 fingerbreadths. A splenic tumor was diagnosed and **splenectomy** performed, with recovery. The organ measured 10 by 3 inches, had a greatly thickened capsule, and weighed 4125 Gm. Its center was filled with a network of connective tissue enclosing blood clots, and the parenchyma of the organ was peripheral in situation. Histologically the condition proved to be cavernous angioma with hemorrhages and thromboses. The tumor is thought to have been congenital and developed gradually. E. Steden (Arch. f. klin. Chir., cxxx, 616, 1924).

**Mesentery.**—A very unusual case of venous cavernous angioma of the mesentery, complicated by intestinal obstruction, has been reported by Juilliard, of Geneva. He collected 78 cases of mesenteric tumors of all kinds and this was the only case of angioma reported. It was situated in the mesentery of the duodenum and caused acute intestinal obstruction, which ultimately proved fatal. The clinical, pathologic, and surgical bearings of this unique growth were thoroughly discussed by this author.

**Ovary.**—A very rare and probably unique case of angioma simplex has been reported by Jacobsen. It formed on the surface of the right ovary of a woman, aged 35, who had borne 2 children. The tumor ruptured with fatal hemorrhage into the abdominal cavity.

**Placenta.**—Tumors characterized by the new formation of blood-vessels have been observed to occur in the placenta, representing the curious phenomenon of a new growth within a new growth. The various types under which this new formation of vessels may manifest itself were described by Kraus, who classified certain tumors of the placenta as hemangiomata because the bulk of these growths was made up of blood-vessels. The connective-tissue elements were only increased to the extent required for the support and framework of the tumor substance. The condition consists essentially in the alteration of a circumscribed capillary area. The growth is sometimes encapsulated and may originate at any stage in the formation of the placenta.

The location of the tumor is in the chorionic villi and their ramifications. As a rule, the angioma endangers the life of the fetus through disturbance of the fetal circulation.

**GENERAL DIAGNOSIS.**—The characteristic appearance of simple nevi renders the diagnosis easy and positive in the majority of cases. They may occur in any portion of the body, but are relatively rare on the abdomen and thorax. The seat of predilection is the head, especially the face. In cavernous angioma, other important diagnostic features are the compressibility of the growth and its capacity to swell and become

turgid; hence, "erectile tumor." The tumor mass is soft and yielding, compression serving to diminish its size and lessen the discoloration. Upon removal of the pressure, the blood returns into the tumor and the former appearance is re-established. The tumor becomes noticeably larger by lowering and compressing the affected part. These various pressure changes are not obtainable when the growths contain calcified angioliths or much adipose tissue. If there is a communication with larger arterial vessels, pulsation may be added as another characteristic. A plexiform angioma is usually unmistakable on account of the tortuous and pulsating arteries, which can be readily palpated, and the irregularly outlined distribution of the neoplasm.

Circumscribed angiomatous growths in muscles are rarely larger than a nut or a hen's egg. The size of the tumor is not so readily determined when the distribution is diffuse. Since these muscular growths are absolutely independent of the skin, this is freely movable above them, a sign of considerable diagnostic importance. The consistence is variable, and they may be as hard and irreducible as fibromata. When the growth is felt to be very firm on pressure, it is sometimes found to contain calcareous concretions (angioliths), whose presence may assist the diagnosis, though more often they confuse it by suggesting osseous or chondroid functions, as in sarcoma. As a rule, however, they are somewhat doughy to the touch and sometimes apparently reducible, depending to a certain extent upon the relaxation or contraction of the affected muscle. The Esmarch band-

age applied to the root of the limb in certain cases determines a diminution, and in others an increase, in the volume of the tumor. The differential diagnosis from intermuscular sarcoma is sometimes very difficult, the slow course of angioma being the most important distinction. The diagnosis of vascular tumors of bone is impossible during life, on account of the close resemblance to osteosarcoma.

Circumscribed painful angioma is a variety of vascular tumor which is almost invariably situated in the extremities, especially the upper arm and forearm, but also the leg. The differential diagnosis from other painful tumors is based upon the rough and irregular surface, the bluish discoloration of the skin, and moderate dilatation of the subcutaneous veins in the surroundings. The growth is soft in the beginning and only becomes painful as the result of induration with pressure on the nerves. Broca describes a case observed by Verneuil (scaphoid bone of tarsus) which was particularly characterized by severe pain.

**GENERAL PROGNOSIS.**—Angiomata are benign in character, but their behavior is extremely variable. They may remain stationary or show a tendency to subsidence, while others suddenly start to grow, either spontaneously or as the result of traumatism. An obscure influence of pregnancy and menstruation has been noticed in this connection. Ulceration is not of common occurrence. In the absence of complications (inflammation, ulceration, hemorrhage, transformation into a plexiform angioma), simple superficial vascular growths have a very favorable prog-

nosis as far as health and life are concerned. A spontaneous cure sometimes results as the sequel to inflammatory changes. On the other hand, the prognosis must always be guarded as to the outcome of a given treatment when the growth is other than very small, circumscribed, and superficial. Left alone, simple vascular tumors usually persist in their original size and color, but there is a certain danger of transformation into plexiform angiomas. The danger of ulceration and hemorrhage is greatest in the tumors exposed to frequent contact and friction. The prognosis of cavernous and plexiform angiomas is more serious, on account of the tendency to inflammation of these tumors, with septic thrombophlebitis, pyemia, and death. Moreover, there is the risk of sudden and sometimes alarming increase in size, and in view of this possibility it is advisable to keep all these growths under observation for the purpose of timely interference should this become necessary. In general terms, the prognosis is dependent upon the seat and extent of the growth, as well as the importance of the organ or organs involved in the angiomatous process.

**TREATMENT.**—The aim and object of the surgeon in the treatment of all forms of angiomas is: to obliterate the vessels which constitute or nourish the growth, as by peripheral ligation or by compression; to destroy the growth with all its constituent elements by the interstitial action (necrogenic or vasculo-oblitative) of irritating, caustic, or other agents applied externally or introduced into the affected tissues; by the extirpation or excision of the angiomatous area in its totality. For

the accomplishment of these purposes a great number of methods have been recommended, some very valuable and practically useful, others very impractical and scarcely worthy of mention. In the selection of the method of treatment the surgeon must be guided largely by the special needs of the individual case, the nature of the growth, its situation, extent, depth, the organ or parts involved, complicating conditions (malignant associations, etc.). He should also be guided by the sex (in determining the effect of mutilating or disfiguring operations, on the face especially), the age, and general condition of the patient. In general terms, excision or extirpation is the *method of election* in all growths of limited extent which are well circumscribed and defined when they are situated in parts which can be sacrificed without involving disfigurement or the loss of important or vital organs. Sometimes extirpation—including amputation, in the extremities—is a *method of necessity*, the extent of involvement of the affected parts being so great that no conservative procedure is possible. Some of the methods recommended, such as ligation of afferent arteries, are only palliative, simply diminishing the growth of the tumors, and not radical; hence, the treatment may also be classified as radical and palliative. In a general way, the agencies employed to accomplish the objects of treatment, whether palliative or radical, may be grouped as follows:—

**Compression Methods** (direct mechanical compression with pads, adhesive plaster, acting by pressure in superficial nevi; collodion).—In very mild cases, and then only in very

young children, compression of the growth, or of the vessels leading to it, is recommended on account of its simplicity; but, as a rule, the effect is very slight and transitory after the infants are more than 3 months old. It is well proved that, in very young children, arterial angiomas and venous, as well as capillary, nevi are amenable to a cure by prolonged gradual compression.

Direct pressure with a disk of "sponge rubber," adapted to the size and contour of the growth or blemish, about  $\frac{1}{2}$  inch thick, and held in place with a firm bandage, is the simplest, safest, and often the most efficient method of removing these blemishes in the newborn infant.

As advised by the late Dr. Stelwagon in his book, "Diseases of the Skin," the rubber pad is fastened to an elastic bandage—not the plain rubber bandage, but a loosely woven garter-like bandage, devised by G. H. Fox, of New York, and obtainable in the shops. The pad should be kept on constantly, only removing it to readjust it. This pressure plan is most successful in the first three months of infantile life, and should be given a fair trial whenever it is at all applicable. In other cases the pressure principle is more easily carried out by painting the surface 2 or 3 times daily with a mixture of 1 part of **ichthyol** to 9 parts of **collodion**. The nevus becomes compressed underneath the resulting pellicle until the rapidly growing surroundings have caught up with the excessive growth of the vascular tumor.

**Superficial cauterization** with caustics, **sodium ethylate**, **fuming nitric acid**, **carbolic acid**, **zinc chloride**, **corrosive sublimate**, **caustic pastes** (ar-

**senic and zinc chloride**, **potassium hydroxide**), the **thermocautery** and **galvanocautery**.

**Zinc chloride** has been especially recommended for the purpose, as superior to all other methods of treatment, by Neumann, based upon practical experience with 700 cases. The remedy, in the form of a 5 or 10 per cent. sol. in flex. collodium, well shaken up, is painted on with a fine brush; it will in many cases prove sufficient to produce the mortification of the entire growth. Its action may be assisted by the addition of **arsenic** or **chromic acid**. In case of partial failure, the remnants of the growth should be covered with an **arsenic paste** (acidi arseniosi et sulph. depur.,  $\bar{a}\bar{a}$  4.0; ung. cerei, q. s. ad 100.0). This paste may be left in place for eight to twelve days, under aseptic dressings, the remnants of the growth becoming detached in the interval, leaving a smooth, slowly granulating wound surface. Or the necrotic portions may be removed at the end of the first forty-eight to seventy-two hours with a sharp curette. There is no danger of hemorrhage, provided the preliminary treatment has been of sufficient intensity. On account of its toxicity, the surface treated with arsenic paste should not be too extensive; it should be remembered that the action of arsenic is not only local, but progressive (gangrene). Although this contingency hardly enters into consideration in ordinary cases of telangiectasis and hemangioma, the arsenic paste may be supplanted by parenchymatous or interstitial injections of dilute **zinc chloride**, which has no toxic effect. Surfaces measuring 30 to 40 sq.cm. and over may be destroyed at one

time without fear of absorption. The danger of infection is inconsiderable (none in 700 children treated by this method). Parenchymatous injections are especially applicable to those cases in which the emulsion treatment cannot be carried out, as, for instance, in the mucosa on the inner surface of the lip.

In his zinc choride treatment, Neumann applies an emulsion of from 5 to 10 parts of **zinc chloride** in **collodion**, to make 100 parts. A piece of adhesive plaster is first placed over the angioma, with a hole corresponding to the lesion, but somewhat smaller, as the action of the chloride extends a little way under the edges of the plaster. This dressing is removed the next or on the second day, and the lesion cleansed and left to nature under a fresh, merely protecting dressing. The defect usually heals rapidly, sometimes in a week. If residua of the angioma still persist, he applies the arsenic and sulphur ointment. The sound parts are protected with fenestrated gauze, and this paste is applied on another piece of gauze. In two or three days this dressing should be removed. Zinc chloride in the above dosage has no toxic action, and no absorption need be feared, even on an area of 30 or 40 square cm.; the arsenous acid, however, may cause toxic effects. When possible, he substitutes parenchymatous injection of zinc chloride.

Skin angiomas can be eliminated by **puncture** followed by application of 1 or 2 drops of **collodion**. The latter, contracting, prevents return of blood into the tumor. This method was used with success in a child with multiple angiomas in different parts of the body, some of the size of a fingernail. A drop of collodion was applied to

each every 2 or 3 days. H. Krüger (Zent. f. Chir., Nov. 17, 1923).

*Fiorani's method* of removing nevi consists in the application of **corrosive sublimate** dissolved in flexible collodion. Several applications may be required, and a 13 per cent. solution is recommended. Dressings are unnecessary and the nevus may be allowed to atrophy undisturbed after the desired caustic action has been produced.

**Cauterization** with **fuming nitric acid** is a simple and efficient remedy in certain superficial nevi, producing a scab of sufficient depth, which becomes spontaneously detached and leaves a smooth, delicate cicatrix in its place. During the cauterization, the surrounding skin should be carefully protected with strips of adhesive plaster. This form of treatment is not adapted to nodular nevi or growths which are raised above the skin surface or distributed subcutaneously.

Ogata, a Japanese surgeon, recommends the following preparation as a local application for the removal of nevi and telangiectases. **Rice grains** are washed and placed in a glass dish; 10 per cent. **potassium hydrate** solution is poured over them, and they are allowed to stand six to eight hours after they have become thoroughly softened. The starch of the rice grains swells up and gradually becomes transparent. When the grain has become entirely clear the alkali solution is poured off and the deposit is washed with water. The mass so obtained is triturated in a porcelain mortar and forms a colorless, sticky mass, strongly alkaline in reaction, and consisting of a combination of starch with potassium hydrate.

Through the union with the starch the caustic properties of the alkali are considerably reduced and the tissues are not invaded too deeply. The preparation loses its strength in about six hours and therefore must be freshly prepared. It is applied by means of a pointed glass rod after the skin has been cleaned with tincture of soap and dried off. Several applications can be made at a single session, the area being washed with **sterile salt solution** each time after the caustic applied has dried. In children it is advisable to apply 5 per cent. cocaine solution before the caustic. In most cases 3 to 5 applications are sufficient, the area treated becoming black and being cast off in from seven to ten days. The scars are at first red, but later whiten and become entirely invisible. It is important not to treat too large an area at a time; otherwise, disfiguring scars due to suppuration may result. Lesions of considerable size require a treatment of months or even a year.

**Freezing** by the application of **liquid air** has been very successfully utilized in the treatment of superficial nevi and other growths.

On account of the practical difficulty in the way of readily obtaining and handling liquid air, "**carbon dioxide snow**" has come into general use, since this mode of treatment was first introduced by Pusey.

Small non-pigmented moles can be easily removed by **freezing** for periods varying from 40 to 60 seconds, according to their apparent depth in the subcutis. The ensuing blister should be pricked aseptically and then dressed with calamine lotion. The scab should never be forcibly removed, but allowed to separate spontaneously. The procedure may need repetition.

Hairy moles, if very small, should be treated by **electrolysis** of the individual hairs. The pigmented elements tend to fade as the hair-bulbs are destroyed. Remaining pigmentation can be dealt with by **freezing**. For larger moles, especially when warty, **excision** followed by grafting or the application of **diathermy** are the methods of choice. Radium, the X-rays, the cautery and chemical caustics are not advised in this type of mole. Once decided upon, radical procedures should not be postponed, as moles grow with the growth of the child. H. C. Semon (*Lancet*, June 27, 1925).

The procedure as carried out is as follows: From a cylinder of carbon dioxide such as is used in making frozen microsections, a fairly strong jet of the gas is played on to a piece of cotton-wool; the rapid evaporation of the cotton-wool causes intense chilling, which condenses a portion of the gas into a snowy powder with a temperature of 70° C. Some of the solidified gas is applied to the surface of the nevus, where it remains from ten to twenty seconds. The intense cold causes extreme contraction of the blood-vessels and anemia of the growth. This is repeated once or twice in the same sitting, the white flakes being applied to the different parts of the vascular surface. The snow may also be molded into suitable applicators. Pusey stamps it into an ear-speculum or into cylindrical hard-rubber tubes of different widths. With the former, one has a cone-shaped cylindrical mass which permits a freezing surface of variable size according to the lesion to be treated.

The applicator employed is best handled through a piece of chamois skin or through a glove. The duration of the freezing should correspond

to the intensity of the effect desired. Superficial lesions can be destroyed in from five to ten seconds. Deep-seated growths, whose thorough destruction is contemplated, may be treated even for a whole minute. The physiological effects upon the frozen area vary, according to the time of exposure, from a simple erythema to necrosis. A bulla will form, as a rule, after five to ten seconds of deep freezing when the epidermis is intact. Raw surfaces respond with free serous exudation. "Notwithstanding very energetic freezing, the final result is, cosmetically speaking, eminently satisfactory and the resulting scar is perfectly smooth. It would be difficult to compare the method in this regard to any known form of destruction of tissue, as that of electrolysis, escharotics, caustics, or pure surgical means. This feature, as well as the comparative painlessness, the rapidity of the work, the avoidance of open wound and therefore of infection, makes CO<sub>2</sub> easily the most elegant and safest of all destructive agents (Zeisler).

**Bibliography.**—Pusey, W. A.: *Berlin klin. Woch.*, 1908, xlv, 1146-49; Heidingfeld, M. L.: *Lancet-Clinic*, Cincin., 1908, xcix, 197; Waxham: *Denver Med. Times*, 1908-09, xxviii, 388-393; Zeisler, Jos.: *Jour. Cut. Dis. and Syph.*, Jan., 1909, xxvii; Sauerbruch: *Zentralbl. f. Chirurg.*, No. 1, 1909; Strauss, A.: *Deutsch. med. Woch.*, 1908, xxx, 2312; Low, R. C.: *Carbonic Acid Snow*, W. Wood & Co., N. Y., 1911.

Pusey's treatment of angiomas and nevi with **carbon dioxide snow** used in 250 cases of angioma or nevus, with permanent cure in 93 cases. Nothing compares with the treatment, excepting perhaps radium, the X-rays, and the mercury quartz lamp. The dioxide treatment is simpler and less expensive than either of the above. It

destroys the skin and upper layers of the subcutaneous angiomatous tissue, leaving the epithelium intact. It is applicable to simple superficial angiomas, diffuse red pigmented nevi and brown nevi, and telangiectasia, but not to plexiform angiomas and cavernomas. Salomon (*Deut. Zeit. f. Chir.*, May, 1911).

The face and flexor surfaces are most sensitive to the treatment. Women, particularly blondes, are more sensitive than men, while children are three or four times as sensitive as adults.

Immediately after the application of the **carbon-dioxide snow** the area treated appears white, depressed and hardened, and upon thawing, which requires one to three minutes, an erythema develops. Within two to twenty-four hours a vesicle forms upon the area treated, and this is replaced by a crust in two or three days. In nine to fourteen days the crust separates, leaving a smooth scar of normal color or of a slightly pinkish tinge, which becomes normal within a week or two. During the freezing process the patient experiences but little discomfort, but when the thawing begins a moderate amount of burning is usually felt and sometimes a transient neuralgia develops.

In freezing growths on or near the eyelids a piece of dry cotton should be placed between the lid and the eyeball to prevent the freezing of the latter tissue. The same precaution holds good when growths at the borders of the lips are frozen.

The number of treatments required varies with the severity and depth of the nevus, but in a large majority of cases one treatment will suffice. In the writer's series of cases cures have been accomplished in a large majority of instances, and improvement has been noted in all. Little after-treatment is required, the application of equal parts of zinc-oxide ointment and petrolatum being all that is necessary. G. H. Mize (*Calif. State Jour. of Med.*, March, 1912).

In small hairy nevi, the author uses **electrolysis** to destroy the hairs; bipolar application also removes much of the pigmentation. **Carbon dioxide snow**, carefully regulated by the time of exposure, then destroys the lesion and removes the pigmentation with little scarring. C. Dubois (Rev. méd. de la Suisse rom., Dec., 1921).

**Penetrating, or interstitial, cauterization** with the **electrothermic cautery**; **ignipuncture**; **steam** or **hot air**. While all caustics are inferior to the knife, complete excision may be contraindicated for a number of reasons (deep-seated angioma of the face involving the mucosa of the cheeks; penetrating cavernous tumors of the cranium; extreme youth of patient, etc.). In these cases puncture with the electrothermic cautery may be attempted, provided the growth is not in the face. Not only is the resulting scar very large and unsightly, but more or less considerable loss of tissue is apt to follow, especially around the nose. Moreover, there is always the danger of infection extending to the cerebral meninges from a deep-seated angioma of the face or cranial coverings when inflamed. For this reason aseptic dressings are required until the scab has become detached. As a rule, this form of treatment demands numerous repetitions, either because a part of the growth has been left behind or because there is prompt recurrence.

**Cauterization with hot air** is curative for angiomas and all other vascular growths of the skin, except in cases in which the neoplasm has invaded the mucous membrane, where the knife is preferable. But few sessions are necessary; there is absolutely no hemorrhage; the scar-tissue formed is scarcely visible in small areas. After a few applications the skin becomes mummified, the blood

being driven inwardly. E. Holländer (Berl. klin. Woch., April 23, 1900).

After **ignipuncture**, which is performed with a small needle and repeated at a number of points, a plainly visible and disfiguring scar is sure to remain. The needle should be heated to a dull-red heat, as puncturing with a needle heated to a white heat is likely to give rise to hemorrhage. After the surface has been rendered aseptic, the punctures are made a few lines apart and in a radiating circle, beginning at the periphery and gradually proceeding toward the center of the growth (Hollaender, Snegniereff, Pinkus).

**Steam** and **hot air** have been recommended as useful in the treatment of vascular tumors. In favor of this method it is claimed that the procedure is not only bloodless, but that the cicatrization is perfect and, in the milder cases, practically imperceptible. Vascular tumors in any portion of the body, including the cavities, are amenable to the method. The entire treatment can be carried out in one session. The objection is that a special apparatus is required and that the extent of the burn is not readily controlled.

**Agents which act by coagulating the blood-contents**, exciting aseptic interstitial inflammations, ultimately obliterating the vessels of the neoplasm.

*Electrolysis, Electropuncture, Electrocataphoresis* (Mercuric Cataphoresis).

—**Electrolysis**, especially employed by Kaarsberg in the treatment of vascular tumors, acts by producing coagulation through chemical changes in the blood and in the tissues. The action consists in the combination of a caustic effect at the two elec-



trodes, with dissociation of the water into its chemical constituents. An alkali is produced at the cathode and an acid at the anode, with simultaneous rise of gas bubbles at the two electrodes (oxygen at the anode; hydrogen at the cathode). The danger of pulmonary embolism is inconsiderable, since we are dealing chiefly with hydrogen, and in minute amounts. Electrolysis has a destructive action on vascular tumors through the molecular disintegration of the tissues, with hyperplasia of the connective tissue, while rapid coagulation of the residuary blood takes place. The treatment requires general anesthesia and a somewhat complicated electrical apparatus. Electrolytic treatment was employed with excellent results in over 80 cases by Heuking, who uses the bipolar method, inserting both platinum needles in the tumor. He advocates the method in cases where: 1, the angioma is situated on the face and disfigurement may result from the formation of the scar or contraction of the skin; 2, where the tumor is extensive, especially in cavernous angioma, where surgical treatment might induce severe hemorrhage; 3, when the patient objects to surgical interference.

The advantages of treating nevi early in life are emphasized by the writer. In raised or cavernous-hemangiomas, **radium** in small quantities over long periods of time yields satisfactory results. **Desiccation** and **carbon dioxide snow** are used to best advantage in flat *pigmented nevi*. In *raised verrucous nevi*, hard or soft, **radium**, followed by **carbon dioxide snow** or **desiccation**, are advised; in soft moles, **electrolysis** or **desiccation**. In *port wine marks*, the **Kromayer** and **Finsen lights** give the best results. R. H. Stevens (Jour. of Radiol., Nov., 1921).

Telangiectasis is best treated by **electrolysis**. Not all angiomas respond equally well to **radium**. The port wine mark is very obstinate, the flat nevi generally being more refractory than the raised. Many nevi of small size situated on covered parts are easily destroyed by more rapid methods. The scar following the skillful use of **carbon dioxide snow** is often insignificant. **Surgery** often gives brilliant and rapid results. In certain selected, raised vascular nevi of the face, **radium** therapy yields results which probably cannot be achieved by other methods, especially if begun in early infancy. Rulison and S. McLean (Amer. Jour. Dis. of Childr., May, 1923).

**High-frequency treatment** has been successfully employed in cases of telangiectasis, in applications of five to ten minutes' duration each (Bulkley, Pfahler). Margaret Sharpe recommends a vacuum electrode of her own designing: "It is exhausted to a much higher degree than those usually made for use with the high-frequency current. It gives a bright-green fluorescence, even in daylight, gives off no sparks or perceptible brush discharge, does not heat, and imparts no sensation whatever to the skin, which does not redden. It is held in contact with the skin, some pressure being used in the case of nevus."

*Coagulating and irritating injections of chemical substances* (ferric sesquichloride, Piazza's fluid, carbolic acid, zinc chloride, chloral hydrate), mentioned only to be condemned. Parenchymatous injections of ferric sesquichloride especially have been known to cause suppuration, a most serious complication when there exists a communication with the brain. Thrombi may become detached and may be carried to the brain and lungs, with a fatal outcome.

**Boiling-water Injections (Wyeth).**

—Boiling water has been successfully injected in a number of cases of superficial capillary angioma, with very slight subsequent scarring. Wyeth had a special syringe manufactured into which boiling water is drawn directly, and if necessary can be heated afterward over a gas burner. The instrument is to be handled with asbestos gloves. The method, according to him, is a homemade, simple, and entirely aseptic procedure, which commends itself for certain otherwise discouraging intractable cases.

Wyeth's method of treatment of angiomas by injections of boiling water, about 30 to 60 minims (2 to 4 c.c.) at a time, had no failures in a series of 26 cases. In every instance the results have been gratifying. Most of the lesions were on the face and scalp. Four patients had angiomas on the tongue, ranging from the size of a filbert to that of an English walnut. One had the lesion on the left gluteal region as large as a cocoanut; another patient presented a fusiform angiomatous growth on the right middle finger between the second phalangeal articulation and the knuckle, which tumor caused great pain. F. Reder (Jour. Amer. Med. Assoc., Jan. 30, 1915).

**Alcohol Injections (Schwalbe).—**

The underlying principle of this method is the local inflammatory reaction of the tissues, followed by sclerosis of the connective tissue with compression and final obliteration of the blood-vessels. The injections (1 to 4 cm. of 70 to 80 per cent. alcohol) are administered at intervals of several days, beginning at the periphery of the growth and gradually proceeding toward the center. Caution is required as regards the management of those portions where the skin is thinned out, since these localities are extremely liable to necro-

sis, with inflammation and hemorrhage. It is claimed in favor of the method that alcohol injections leave no scars, and also that they produce very little pain, so that general anesthesia is superfluous. The simplicity of the procedure permits its employment without special preparation or complicated apparatus, all that is required being a Pravaz or large hypodermic syringe.

**Injection of hydrogen peroxide (Moseitig-Moorhof),** which acts chemically and mechanically. The introduction of hydrogen peroxide into cavernous tumors is followed by grave alterations of the blood, especially when considerable amounts are employed. The hydrogen peroxide is almost instantaneously broken up into oxygen and water by the blood, with marked evolution of foam, which is accompanied by the coagulation of the fibrin contained in the blood. When the contact is prolonged the hemoglobin leaves the red blood-corpuscles and becomes dissociated. The coagulant effect of the remedy is probably accounted for by these chemical processes. Dangerous and sometimes fatal gas embolism in the lungs may follow the introduction of large amounts of hydrogen peroxide into the circulation.

The introduction of magnesium darts or rods (Payr's method). The indications for this form of treatment are based upon the accurate understanding of the pathologic-anatomic peculiarities of vascular tumors. The treatment does not involve the danger of thrombosis or embolism, and complications due to infection have not been observed. The growth becomes obliterated without any disturbance of the general health, and the cosmetic results are claimed to be excellent. The minute orifice through

which the magnesium is introduced later on becomes entirely invisible. The treatment offers the advantage of a very simple technique, permitting its performance under local anesthesia with little assistance and no loss of blood.

The Payr procedure is especially adapted to the treatment of vascular tumors of the subcutaneous cellular tissue. Very superficial cutaneous growths are less accessible and present far greater technical difficulties. Vascular tumors involving the mucous membranes are least suitable, on account of their delicate coverings as well as the constant friction and irritation of the parts (mucosa of lips and buccal cavity in general). This form of treatment finds its chief indications precisely in those cases where the cosmetic problem is most serious (simple and cavernous vascular tumors at the chin, cheeks, ears, the surroundings of the eye, at the forehead, and at the neck).

The method, which is partly chemical and partly mechanical in its action, consists in the introduction of rods or arrows of magnesium in all directions, by way of a small incision in the skin. Subcutaneous vascular tumors of the cavernous type are especially well adapted to the magnesium treatment. Extensive processes of coagulation take place after the magnesium has entered the large blood-spaces lined with endothelium, and these processes are readily transmitted to the vicinity through the communications of each individual blood-space. When the cavernous tumor has been treated with a sufficient amount of magnesium, the result is extensive thrombosis, terminating in complete obliteration through organization of the clot. An essential requirement of success is that the metal be distrib-

uted as uniformly as possible in every portion of the growth. The magnesium darts should be arranged, as they are thrust into the tissues, somewhat after the pattern of a fan, so that all the parts of the cavernous tumor are interspersed with the metal. Magnesium is decomposed in the tissues with considerable evolution of the hydrogen gas (1 gram of magnesium will yield 1 liter of hydrogen). Hence the possibility that mechanical disturbances, created by the evolution of the gas in the tumor, may enter as a factor in the results of Payr's treatment.

**Physical agents which excite trophic and nutritive changes**, leading to degenerative and atrophic process in the angiomatous area. Chief among these methods are the various light treatments: **sunlight, Finsen, X-rays, ultraviolet rays, and radium.** Attempts to cure with the light treatment have recently been made with some success in cases of superficial angioma. Finsen reported 10 cases of vascular nevi, with 1 complete cure and all the others more or less improved. Pfahler considers that in expert hands the results of radiotherapeutic treatment are at least equal to those obtained by other methods. While it is essential to obtain a reaction sufficient to produce desquamation, there is danger of acting too energetically and producing a cicatrix still more disfiguring than the original disease. The X-ray treatment must not be assumed to have a specific effect on these conditions. It acts by producing a certain degree of inflammatory reaction, which is manifested in the blood-vessels as a proliferative endarteritis, in the tissues.

The well-known degenerative and

obliterative effect of the **X-rays** upon the blood-vessels, which favors the atrophy of the tissues subjected to their influence, would suggest that this mode of treatment is particularly adapted to the cure of nevi.

The theory of the X-ray treatment of vascular nevus is based on the production of scar tissue of such a character as to strangulate the vascular lesions. The smaller the area of vascular dilatation, the better are the prospects of obtaining the desired result through the acute reaction set up in the growth. For this reason this form of treatment is not promising in very large angiomas. During the exposure, the normal parts must be protected with sheet lead and other precautions prescribed by a good Roentgen technique. Comparatively mild ray treatment promises well in cases where the vascularity of the growth is due rather to the existence of a great number of minute or capillary vessels than a few of large size. In all cases dermatitis should be excited, allowed to subside, and excited over and over again if necessary. Unless the reactionary dermatitis is of a very severe character, X-ray treatment is not likely to be successful in cases where the nevus consists of very much dilated blood-vessels. It is in the treatment of extensive superficial nevi that the X-rays promise most. Usually, after each attack of dermatitis, the nevus will be found to have diminished in size, owing to the development of fibrous tissue and the occlusion of the smaller blood-vessels. Irradiation with the X-rays was first attempted by Jutassy, who attributed the successful outcome to a contraction, thrombosis, and obliteration of the

vessels induced by the treatment. While more tedious than most other methods, the X-ray treatment of small nevi or moles has the great merit of painlessness, and the resulting scar is less unsightly than that following the use of the knife or the electrolytic needle.

The **X-rays** should not be employed for flat congenital nevi or port wine stains, but should be restricted to elevated vascular moles and cavernous angiomas, which develop soon after birth and, like other tumors, may grow, at times very quickly. As soon as enlargement is seen, tuberous moles should be subjected to X-ray treatment, preferably before the age of 6 months. The rays should be of medium penetrating power and unfiltered. The writer gives 3 exposures, each of 4 skin units, at intervals of 3 or 4 weeks. In his cases the nevi disappeared without leaving any traces under this treatment. F. Barjon (*Jour. de radiol. et d'électrol.*, Jan., 1925).

**Radium.**—The marked success obtained with radium in the treatment of new growths and cutaneous disorders through great improvements in the methods of its application justified an attentive consideration of its special claims as a cure for nevi and other vascular tumors. Drawbacks of radium as a remedy are, the considerable cost and the expertness and special training required for its successful application. In spite of these drawbacks, which, indeed, have been partly overcome in the period elapsed since the introduction of radium, its use has become widespread by reason of a growing appreciation of its remarkable therapeutic properties.

[Radium has never been isolated. It is obtained from pitchblende, a compound of uranium. What is spoken of as radium is the sulphate, the carbonate or the bromide of radium. Enormous quantities of pitch-

blende have to be worked in order to procure a few grams of the mixed chloride of radium and barium. To prepare a gram of the chloride 10,000 kg. of the mineral must be treated. The commercial value of radium is very high. It is impossible to appreciate the therapeutic value and the possibilities of radium without a general knowledge of its remarkable physical properties.

We will here simply recall the fact that radium gives off heat; that it is phosphorescent; that if it is dissolved in water it decomposes the same into its component parts, but that its main property is its radioactivity. Radioactivity means that the rays given off by radium have the power of penetrating solid and opaque substances; the power of affecting a photographic plate; the power of producing fluorescence, and the power of rendering air and other gases conductors of electricity. In addition, it gives off an emanation which has properties even more remarkable than those of the parent body itself. It is this emanation which gives radium the power of rendering any body it touches radioactive. There are three rays given off by radium, which are known as the alpha, beta, and gamma rays. The alpha rays may exist alone. For instance, polonium, a radioactive substance, discovered by Mme. Curie, gives off only alpha rays. Alpha and beta rays are absolutely distinct and independent; they can exist the one without the other. But the beta rays and the gamma rays are inseparable; they are never found dissociated. The alpha rays are supposed to give off the heat, and they burn. They are capable of producing a very troublesome ulcer of the skin. The penetrating power of these three kinds of rays is expressed as follows: Taking the penetration of the alpha rays as 1, they are stopped by a sheet of mica. The beta rays have a penetrating power of 100, and will pass through a centimeter of lead. The penetration of the gamma rays, on the same basis, would be represented by 10,000; they will pass through one inch of steel. The alpha, beta, and gamma rays have a very close resemblance to the rays which are met with in the vacuum tube used in the production of the X-rays. The strength of radium is estimated by taking uranium as a unit. Radium is then represented by a

radioactivity of 2,000,000; a piece of "quarter strength" will, therefore, have a radioactivity of 500,000. The powdered radium when placed on a disk or plate is covered with a varnish of special make which is unaffected by boiling, by alcohol, or by the heat of a sterilizer. Applied in this way on a flat surface, a few milligrams will go a long way. Radium can be spread on silk or cloth, or anything that can be varnished. It is the sulphate of radium, either pure or diluted with sulphate of barium, which is fixed by the varnish, this salt being chosen in preference to the bromide of radium, as it is insoluble, while the bromide is readily soluble. —R. MATAS.]

A knowledge of the properties of the alpha, beta, and gamma rays is not only essential to meet special indications, but to bring into operation the so-called "specific" or "selective" action of radium, as distinguished from its purely destructive action. This selective action is one of the astonishing things about radium, as illustrated by the manner in which it picks out vascular tissue for destruction. Under its influence, this tissue, as met with in the angiomata, vanishes.

The efficacy of radium was graphically described by Treves as follows:—

"In connection with nevus, let me take four illustrative cases. One is that of an infant with a nevus on the crown of the head the size of a gooseberry. There is no means of dealing with such a growth except by operation. It was cured by comparatively short applications of radium. Here is another case a little more striking: a girl with an angioma of the eyelid the size of a plum. This had been subjected to four operations. Twice it had been excised; twice it had been treated with the actual cautery, but with no benefit. It was perfectly cured by radium without trouble or

discomfort to the individual. Perhaps a more striking case is that of a young woman who had had a nevus occupying the whole of one side of the face. She had been subjected to numerous operations, but with only very imperfect success—I should almost say with no success. But under the influence of radium—and the treatment was, of course, long extended—she was cured. The last case is also remarkable. It was that of a child of 12 with a fibrous angioma situated in the substance of the arm, free from the skin, which was uncovered and sound. The mass was the size of a hen's egg. It was treated with radium from two sides (the 'crossed-fire' method of Wickham and Degrais), and was entirely dispersed in four weeks. It is, I am bound to confess, a little astonishing that a solid mass of such magnitude—not a mere subcutaneous growth—should have vanished so readily."

From experience in over 200 cases the writer concluded that **radium** gives by far the best result in the average run of cases of angioma, and may be easily applied. Occasionally, during the time the reaction is at its height, it may cause some inflammatory condition of the skin; in 1 case measles developed; in another, erysipelas. Care must be taken to guard the part from trauma while the reaction is at its height. He warns, however, that in "port wine stain," a very flat pigmented mole over an extensive surface, radium usually fails and will develop ulcerations, telangiectasis and keloids upon the slightest degree of over-radiation. Newcomet (*Urol. and Cut. Rev.*, Oct., 1920).

In nevus flammeus or port wine mark, gamma and Röntgen rays have practically no effect. **Ultra-violet light** treatment with the water-cooled mercury lamp is better, and radium therapy should be attempted only in small

lesions of dark and evenly distributed color.

Nevus vasculosus, raised from a scarcely perceptible swelling to 2 or 3 mm. or more, when not complicated by a cavernous element, is an ideal subject for **radium** therapy. If slightly raised, evenly colored and smooth, it should be given 20 to 40 minutes' exposure with  $\frac{1}{2}$  or  $\frac{1}{4}$  strength plaque screened with 0.3 mm. brass or the equivalent. If there is any reaction from the first treatment a second should be given in about 3 to 4 weeks. A lead foil diaphragm is used to protect the contiguous normal skin unless the applicator fits the lesion closely. A temporary increase in pigment may persist for several months around the area treated. Telangiectases, if occurring, may be treated with ultra-violet light, the electric needle, or acid. Subsequent treatments, if necessary, should be spread over a considerable time.

Cavernous angiomas are often entirely subcutaneous, in which case they may be entirely or almost colorless. In this lesion the exposure is usually 1 to 2 hours every 4 to 6 weeks over each area. If the lesion is large, cross-firing may be used. Usually 9 months to 2 years are required for a satisfactory result. Tubular applicators may be used, with a little care. A tube screened with 0.5 mm. silver 0.5 cm. from the surface may be left in position to give 25 mg. hr. to each sq. cm. of surface, balsa wood, gauze or light material being used to obtain the distance. Radium gives better results in vascular nevi than carbon dioxide snow or any other agent. Beta rays should be utilized as much as possible, and severe reactions are not justifiable. H. Morrow and L. R. Taussig (*Amer. Jour. of Roentgenol.*, Nov., 1923).

After treating 300 cases of vascular nevi with **radium** the writer believes this method the best available in most cases. Nevi which are growing or have become ulcerated should have immediate treatment. Radiations are used directly over the surface of the nevus. In rare cases—never on the face—emanation tubes may be intro-

duced into the angioma. In extensive nevi, to avoid the production of a checkerboard effect, the treated area is outlined with ink after the exposure. This outline remains until the next exposure; an exact approximation of the edges of each area treated is thus obtained. In flat, superficial vascular nevi it is important to avoid inflammatory reaction, while in flat, deeply infiltrating nevi "toiles" or glazed plaques are used for producing inflammatory reaction. In raised, hard vascular nevi, a mild reaction must be produced in order to level the decolorized tumor; here, too, glazed plaques are used. In the raised soft variety radium is most satisfactory, but inflammatory reaction is to be avoided. With deep, subcutaneous and submucous nevi it is important to place the radium at a considerable distance from the skin and to use relatively large doses. For adults, 500 mc. radium emanation may be placed 6 cm. from the skin. A total exposure of 20 hours, divided into 2 or more periods, may be given. The dosage for infants is 250 mc at 3 cm. for 10 hours, in 2 or more exposures. F. E. Simpson (*Surg., Gyn. and Obst., Mar., 1924*).

The superiority of radium in angioma is due, in addition to the specific effect it exerts on these growths, to its ease of application and absolute painlessness in superficial irradiation. Insertion of radium needles into deeper growths, although approximating a surgical procedure, is nevertheless a minor operation, causing a minimum of pain; it shortens the duration of treatment. The different types of angioma, however, require varying methods. **Electrolysis** may be indicated and prove entirely satisfactory in circumscribed angiomas, particularly in telangiectasis. **Excision** is indicated more definitely in the small, erectile forms of tumor on covered portions of the body. In the cavernous forms, operation is not always devoid of risk, and is not uniformly successful, being frequently followed by recurrence and disfiguring scar formation. In these forms radium is there-

fore preferable. L. Mazzoni (*Giorn. ital. d. mal. ven., lxxv, 920, 1924*).

**Ultra-violet ray treatment** recommended in *X-ray telangiectases*. The proper dosage is that which will produce flaccid vesiculation— $3\frac{1}{2}$  to  $4\frac{1}{2}$  minutes. To be benefited the affected areas should be without marked atrophy and should not be too large. The seriousness of traumatizing tissue already atrophic and degenerative by reason of an agent with a somewhat shorter wave length should be borne in mind. Great care should be taken to prevent infection of the bullæ and erosions produced by treatment. C. G. Lane (*Arch. of Derm. and Syph., Feb., 1926*).

**Surgical Methods.**—The most rapid and efficient means of dealing with vascular neoplasms are operative, and may be subdivided into:—

**Peripheral, subcutaneous (buried) strangulating ligatures** for circumscribed angiomata (Krogus), or the zigzag method (Beck). The application of a continuous series of subcutaneous ligatures in the entire periphery of the tumor is recommended by Krogus in the treatment of plexiform angioma. He proceeds as follows: "Two needles with a handle and flexible point (Lanblin) were employed, one slightly curved and the other more so. The strongly curved needle is introduced first, passing through the skin to the bone, and for a certain distance along the latter, finally coming out again through the skin. The needle is pulled out after it has been armed with a strong catgut thread. Through the same entrance orifice the other (slightly curved) needle is then passed out by the exit orifice immediately beneath the skin; one end of the catgut is threaded in, and the needle is then pulled out. The two ends of the thread are thus made to come out through the same orifice, where they are tied. The

hemorrhage from the stitched channels usually subsides very promptly after the thread has been tied, though it may be very readily controlled by compression. The next ligature is best applied in such a way as to overlap the exit orifice of the former ligature, the ligatures thus acting as chain ligatures without actually interlocking. An uninterrupted series of these ligatures is now placed around *the entire periphery* of the angioma, so as to strangulate, if possible, all the abnormally dilated vessels, thus inducing the shrinkage of the tumor. In case the first operation is not entirely successful, a second and smaller ring of ligatures may be applied around the persistent part of the angioma at a later session. If necessary, the procedure may be kept up until the last trace of the tumor has disappeared. It is of the greatest importance for the success of the treatment that no gap of any size should be left in the series of ligatures. In the originator's experience, these ligatures induce the obliteration of the dilated vessels with subsequent disappearance of the plexiform angioma, without interfering with the vitality of the skin.

A similar method for the treatment of ordinary angiomas was suggested by Karl Beck (Chicago), based on the principle of gradual transformation of the vessel masses into connective tissue. This is accomplished by subcutaneous suture as follows: "A thread of catgut is passed in a zigzag manner first below the skin, then underneath the base of the tumor, then again underneath the skin, underneath the tumor, etc., until the tumor mass is included in this continuous suture. The latter is drawn tight and closed at the point of entrance of the needle. In this manner the circulation is shut off within the tumor,

but no gangrene follows, inasmuch as some blood can yet reach the parts not included in the suture. The mass soon grows smaller and the normal epidermis outside of these limits stretches considerably, but becomes elastic and grows again. This procedure is repeated until the tumor is diminished to the smallest nodule of connective tissue. The hard connective-tissue masses are then excised and the edges carefully united. This treatment applies to all varieties of angioma, but in the arterial and mixed varieties it is necessary to ligate the largest afferent vessels in order to check the rapid growth."

**Ligation of Large Afferent Trunks** (for Cirroid or Other Local Afferent Vessels).—The ligation of the individual blood-vessels has been practically abandoned in the treatment of cirroid aneurism. The method is tedious and uncertain, and gives rise to more disfigurement than an excision scar. It has been successfully employed in cases of venous nevi where excision was impossible. The treatment may be supplemented by the use of strangulating buried ligatures, or injections of alcohol, etc., and firm bandaging, but it is unlikely that these will cure any cavernous tissue persisting after ligation of the main trunk.

**Extirpation or Excision of the Tumor.**—The ideal treatment of angioma is excision. Usually the extirpation of angiomas can be accomplished with comparatively slight loss of blood by attacking them from the periphery within the line of healthy tissue. It should be remembered, as Ribbert has demonstrated, that the angiomas are developed at the expense of an independent germinal bud and remain isolated to a large extent from the surrounding vessels, the diseased tissue



being usually defined by a more or less well-formed capsule. However, the safest course is always to prepare for serious hemorrhage and to make use of every available method of prophylactic hemostasis, including the provisional occlusion of the main afferent artery of the region. The author has found that the preliminary infiltration of the angioma itself and perivascular areas with **physiologic salt solution** containing  $\frac{1}{10}$  of 1 per cent. of **B-eucaine** or  $\frac{1}{5}$  of 1 per cent. **novocaine** and 10 to 20 minims of **adrenalin solution** (1:1000) to the total estimated amount of fluid required to densely edematize the field of operation will be found most useful not only as a hemostatic, but as an anesthetic procedure. The infiltration is obtained by forcing the solution into the tissues under considerable pneumatic pressure by means of the author's special apparatus (see illustration). The solution should be allowed to remain at least ten to fifteen minutes before operating in order to give time for the adrenalin to act in constricting the blood-vessels. The author has always applied this method in late years as a preliminary to the operative treatment of all accessible and well-defined angiomata.

The incision should be made a few lines away from the visible boundaries of the tumor, on the sides as well as its base. A skillful operator will sometimes succeed in removing the growth so quickly that no ligatures will be required until after the extirpation has been completed. Skin-grafting may be required for the covering of the raw surface. In favorable cases (distinctly outlined cavernous angiomata) extirpation of the tumor results in a linear or relatively invisible scar. Complete ex-

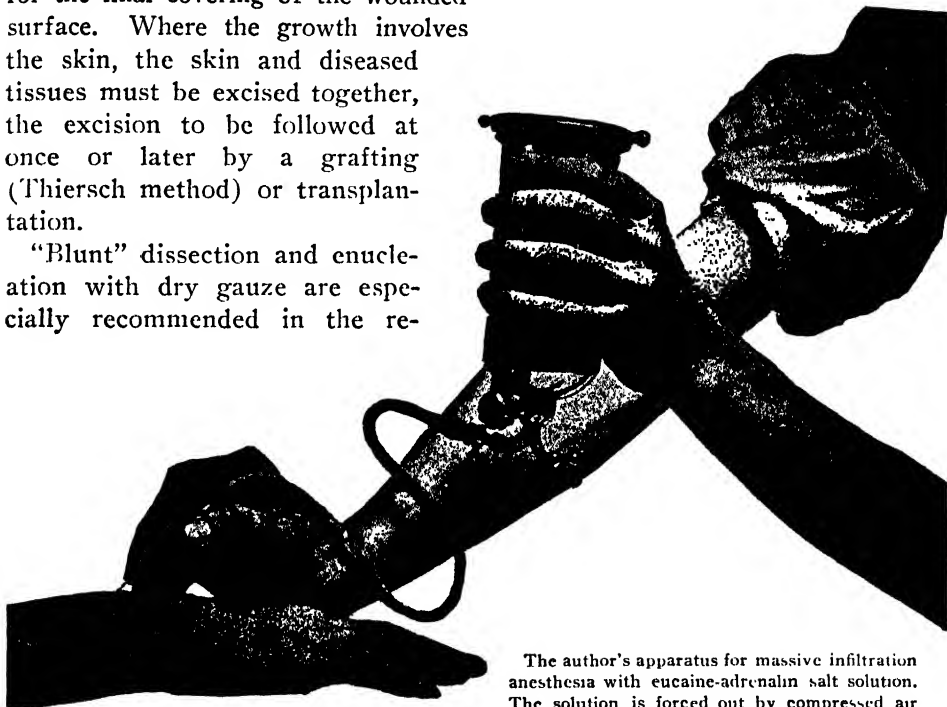
cision is adapted to the superficial as well as the deep-seated and encapsulated forms. When the growth is deep and there is no capsule it may be rapidly extirpated by means of the sharp curette (v. Bergmann), without fear of hemorrhage, since, after the removal of the large blood-spaces, the bleeding remains limited to a few afferent arterics. At the extremities bloodless excision is performed under Esmarch's ischemia, and at other portions of the body with the aid of digital or instrumental compression. A secondary plastic operation may be required for the treatment of remaining tissue defects.

Extirpation is also, according to present experience and statistics, the most important and efficient treatment of plexiform angiomata. The excision of a voluminous plexiform angioma of the head may be aided by previous ligation of the external carotid artery or by temporary compression with soft clamps on the common trunk. The application of a rubber tube around the head, as well as hard-rubber plates pressed to the skull in the temporal fossæ, have been found valuable. Cushing's elastic cranial constrictor is well adapted to this purpose. Circumligation of the tumor, followed in a few days by its extirpation, is justifiable in the aseptic conditions of modern surgery. Daily change of the occlusive bandage is required during the first three or four days following the operation. In the cases where the great extent of the growth precludes the use of the knife, some prospect of improvement is afforded by alcoholic injections. In tumors of moderate size and readily accessible on all sides, excision offers the best outlook. A large plexiform

angioma requires the preliminary ligation of several of the larger vessels. The incision must be made in healthy tissue some distance away from the growth. After the chief nutrient vessels have been exposed, they are caught with hemostatic forceps and divided. Healthy skin is reflected and preserved for the final covering of the wounded surface. Where the growth involves the skin, the skin and diseased tissues must be excised together, the excision to be followed at once or later by a grafting (Thiersch method) or transplantation.

"Blunt" dissection and enucleation with dry gauze are especially recommended in the re-

over the convexity of the tumor, if the superficial part of the skin is relatively healthy and participates but slightly in the formation of new vessels. A marginal incision is made where there is extensive vascularization of the skin. The periphery of the tumor is exposed under compression, followed by pene-



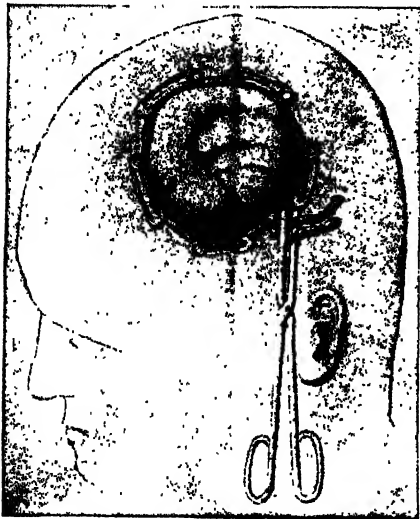
The author's apparatus for massive infiltration anesthesia with eucaine-adrenalin salt solution. The solution is forced out by compressed air forced into the cylinder with a hand pump.

moval of certain cases of well-defined subcutaneous angiomata. The method is especially adapted to cases of large cavernous angiomata, simple angioma after it has assumed tumor proportions, and cases of mixed angioma in which all three varieties of vessels are represented. Even in enormous tumors in which other excision methods are inadmissible as too dangerous, the systematic and careful blunt and "dry sponge" dissection of all the prolongations of the growth may yield favorable results. An incision is made

of the deeper portions. Bleeding arteries or veins are caught up and tied. Not a single ligature may be required when the border of the capsule of the angioma is closely adhered to, so as to operate in healthy tissue. Dry "gauze" dissection is not so well adapted to the treatment of plexiform angioma.

**Körte's method of extirpation (especially for plexiform angioma).** Control of the hemorrhage is the main difficulty encountered during extirpation, and various methods

have been devised to diminish the amount of bleeding. Different procedures calculated to meet this difficulty have been studied and discussed by W. Körte. He found that an elastic head bandage was of little avail in most cases, while previous ligation of the main trunk which supplies the tumor greatly diminishes the bleeding; if it is an angioma of the head the external carotid is tied. Of course,



Elastic constriction of the surface with the aid of transfixion ("safety") pins, applicable in the removal of large vascular tumors. (Senn.)

this does not empty the tumor entirely, as a collateral circulation sets in, and as some of its content is supplied through the skull. In addition, he passes a mattress suture through the skin around the entire tumor, about 2 cm. from its base; the growth is then extirpated within this suture, when the latter is removed and the bleeding vessels are ligated, the defect being closed by bringing the edges of the wound together. If the growth is very large, the skin edges cannot be brought together and the skin over the tumor must be pre-

served. After ligating the main trunk as before, the mattress suture is not passed all around the tumor, but in horseshoe-shaped fashion, and digital compression is made at the point (pedicle of the future skin-flap) where the mattress suture has been omitted. An incision is then made down to the periosteum just inside the suture line, when skin and tumor are rapidly dissected up together, the bleeding from the bone being easily controlled by gauze and pressure. The angioma can then be slowly dissected from the skin with practically no bleeding, while, if the skin were first dissected from the tumor before the latter was raised from the periosteum, the bleeding would be more profuse. The mattress suture is then removed and the vessels tied as before, and the skin-flap is sutured in place. Körte usually also extirpates the afferent vessels as well, but thinks the procedure unnecessary, as they get smaller spontaneously after removal of the main tumor. Extensive racemose angioma on the extremities offers greater difficulties, as the tying of the large number of vessels which require this may give rise to gangrene, so that amputation must be considered in the treatment of such tumors.

A new procedure for the obliteration of superficial vascular nevus was devised by L. L. McArthur, consisting in a section of the integument on a plane horizontal to the affected surface, in such a way that the entire thickness of the integument is not destroyed, but that the knife passes through each capillary loop as it comes to the surface. The idea is to preserve sufficient intact integument to prevent its actual perforation with protection of the con-

nective tissue beneath. Application of thin Thiersch grafts after the blood in the undivided capillaries has coagulated results in obliteration of the divided capillaries through plugging with blood-clot, and the graft, becoming organized, conceals the pigmented appearance of the blood-mark. The method was successfully adopted in a case which had already been treated by electrolysis and in which other procedures for the destruction of the vessels had been applied without benefit.

**Amputation.**—There are certain extreme conditions which, in spite of all treatment, remain a constant source of danger on account of progressive growth, pressure on the surroundings, hemorrhage, and suppuration. Under these circumstances any form of treatment which does not completely and radically destroy the growth only aggravates the condition by stimulating the vessels to increased proliferation and extension. The sacrifice of the affected extremity by amputation becomes then a matter of necessity.

**Summary.**—The foregoing methods may be summarized as follows: On all newborn babies with well-defined "mother's marks" or limited angiomata, first try direct **mechanical compression** by Stelwagon and Fox's method; then **collodium** and **ichthyol** as a second choice.

If these procedures fail, as they may in older infants, one may try, according to circumstances and available resources, applications of **carbon-dioxide snow**.

If **radium** is available, its application by the most recent technique should be preferred over all other methods, in the hands of a thoroughly competent expert, as the most satisfactory treatment.

The superiority of radium deserves particular recognition when the nevi occupy conspicuous places and invade the vicinity of important organs (eyes, nose, ears). When radium is not available, the **X-rays** and **electrolysis** are worthy of trial. In the more superficial and deep-colored nevi, **superficial cauterization** obtained with application of a **zinc chloride emulsion** (Newmann) or a **bichloride collodium paint** (Fiorani) or even **Ogata's Japanese caustic** is well worthy of trial. Whenever a well-defined circumscribed and elevated angioma can be surgically removed without disfigurement, deformity, or danger to life, it is best—after a fair trial of the bloodless methods previously mentioned—to **excise** the angiomatous mass after a previous massive anesthesia and ischemia with a beta-eucaine (or novocaine) adrenalin saline solution injected by the author's method.

When the usual methods of prophylactic hemostasis are unavailable, and it is evident that a surgical extirpation would be hazardous on account of hemorrhage or involvement of important organs, the bloodless methods of tissue strangulation by the **buried ligatures** of Krogus, Beck, and others should be considered. In some cases a combination of methods may accomplish the best results, the strangulation of the tumor by ligatures being preceded or followed by a course of interstitial sclerogenic injections induced by **alcohol** or Payr's **magnesium darts**. It is in the large cirroid aneurisms of the head and scalp, which involve widely diffused arteriovenous plexuses, that the resources and ingenuity of the surgeon are the most seriously taxed. It is only in the extreme, almost monstrous, types of this disease (plexi-

form angioma) that nothing but a merely palliative course can be pursued. Fortunately these extreme cases are likely to become still less frequent in practice as the advantages of early treatment become better known.

Whenever ulceration and hemorrhage threaten life, provisional hemostasis may be obtained by direct **mechanical compression** over the bleeding point, the pressure being applied over a non-irritating antiseptic hemostatic powder held in a sterile bag or sachet, which will form a firm scab and remain in place until granulations have developed (**ferripyrrine**, **Squibb's compound alum powder**, etc.); or the bleeding may be promptly arrested by suturing the bleeding area percutaneously pending more definite and radical measures. The ligation of the main artery of the region involved is, as a rule, only a palliative measure which is rarely of value except as a provisional hemostatic or denutrient, to starve rapidly growing tumors.

The injection of **quinine and urea hydrochloride** has been resorted to with success by W. Wayne Babcock (N. Y. Med. Jour., Mar. 3, 1917) for the destruction of angiomas and other new growths.

While the injection causes intense though transient pain, marked secondary edema, a sluggish ulcer, a transient induration, and there is the possibility of quinine idiosyncrasy, the advantages are: The intensity of the necrosis produced, even in very vascular tissue; a secondary persistent anesthesia; the low toxicity of the drug, and the convenience of the application especially upon mucous surfaces or other regions not readily accessible.

The technique followed by the writer is as follows: An ordinary hypodermic syringe is employed, and for convenience, a 33 per cent. and a 50 per cent. solution of quinine and urea hydrochloride is prepared in ampoules containing 2 c.c. (32 minims) each. With a fine needle the affected area is infiltrated (not too widely). The chief action of the injection is to block the circulation

and cause ischemia; therefore, the entire area is infiltrated, or a proximal infiltration is so given as to cut off the blood-supply. In sensitive areas the preliminary injection of a  $\frac{1}{2}$  to 1 per cent. **novocaine solution** may be desirable to prevent the initial pain.

Over 300 benign pigmented moles were treated by **excision** or the **cautery** without a recurrence or death from metastasis. In excising, a margin of at least  $\frac{1}{2}$  inch should be given; the skin and fat should be cut through and some of the fat removed. **Procaine** anesthesia usually suffices. Where it is difficult to give a good margin, *e.g.*, near the ala nasi or eyelid, the cautery, hot enough to cut through the skin readily, should be used. Out of over 200 operated cases of *malignant* moles, only one 5-year cure was obtained. J. C. Bloodgood (Jour. Amer. Med. Assoc., Aug. 12, 1922).

All angiomas should be regarded as potentially malignant by extension. Prophylactic destruction of angiomas as soon as recognized is advisable; the younger the child, the more favorable the prognosis. Elevated growths yield to **freezing** or **radium**. In the cavernous type, complete **excision** is best; in the racemose type, **ligation** or, preferably, **excision**. The authors report a case of multiple angiomas of the internal popliteal nerve and other soft tissues of the left leg in which pain and functional disturbance were such as to require amputation. Deep radiation in infancy might have avoided the loss of the limb. S. F. Stewart and M. E. Bettin (Surg., Gyn. and Obst., Sept., 1924).

In pigmented nevi of the face, it is best to make first repeated **excisions** of fragments of the skin. When, with extensive lesions, the maximum area has been excised without producing traction on the surrounding parts, recourse to **skin-grafting**, especially the dermo-epidermal graft, becomes necessary. J. N. Roy (Arch. of Otolaryng., Dec., 1925).

RUDOLPH MATAS,  
New Orleans.

## BONES, DISEASES OF. RICKETS, OR RACHITIS.

The term "rachitis" should be dropped, as it implies an inflammatory process which does not exist, modern research having shown that rickets is a deficiency disease.

**DEFINITION.**—Rickets is a disease of infancy and childhood due to deficiency, in the osseous system especially, of substances required for the normal development of bone and other tissues—phosphorus and calcium, the former element in particular.

**SYMPTOMS.**—Sweating, especially of the head, irritability, nocturnal restlessness, anorexia and constipation, are often observed early in a given case. Muscular atrophy is indicated by inability of the child to hold up its head, sit erect or crawl at the usual age, and there is often an enlarged abdomen, due to relaxation of the abdominal muscles. All muscles, in fact, are flabby and fail to support the body; those of the feet failing to support the arches, the child is flat-footed.

The bones and joints are the seat of the most striking and characteristic phenomena. The joints, particularly those of the elbows, knees and ankles, become unusually sensitive, and cause considerable pain if the child is not handled with the utmost gentleness. The joints are rough and thickened on palpation, aside from the softness of the overlying fat. There is enlargement and increased vascularity of the epiphyses. The tissues adjacent to the osseous shaft become enlarged, owing to thickening of the periosteum. The radius, tibia, vertebræ and ribs are especially affected. The "pigeon-breast" or projecting sternum, and "Harrison's

groove," a curve reaching from the ensiform cartilage on each side to the axillæ and due to loss of support, by the softened ribs, of the diaphragm, which pulls inward along the curved line, are features of severe cases. The ribs on palpation also feel irregular, forming the familiar "beading" or "rachitic rosary" observed early in such cases. The bones of the legs, especially if premature perambulation is attempted, soon show, owing to the weight of the body carried by them, evidences of softening by becoming "bow-legged" "knock-kneed," etc., as is often observed in negro children.

The skull and spinal column are prominently involved in the morbid process, the former especially. Owing to its relative softness, the calvarium may be irregular in shape, the top being lower than normally, with open and large fontanelles merging in with the sutures. The forehead may project anteriorly and the parietes show prominences, forming "bosses," which cause the head to appear square, though irregularly so. The roundish areas of depression due to the softness of the underlying bone, known as "craniotabes," are also present in severe cases. This condition is not typical of rickets, however, being often observed in other disorders, notably hereditary syphilis.

The writers studied 129 infants with craniotabes and concluded that this symptom, before the age of 4 months, is generally not due to rickets, whereas after this age it is associated with rickets in at least 75 per cent. of cases. Of 14 infants who developed bow-legs, 14 were not rachitic according to laboratory and clinical criteria. While craniotabes usually responds to antirachitic treatment, bowing does not yield readily to the same measures.

There seems to be no distinction between rachitic and non-rachitic forms of this deformity. Barenberg and Bloomberg (*Amer. Jour. Dis. of Childr.*, Dec., 1924).

In a study of craniotabes the writers found that the age incidence was earlier than that of rickets. Season had a definite influence on its occurrence, the greatest number of cases appearing in May, June and July. Exposure to sunlight had a marked beneficial effect. In 42 per cent. the areas became calcified at the end of the first month, and in 91 per cent., at the end of the third month. Season had a definite influence on the disappearance of craniotabes, 93 per cent. of the patients being cured in August and September, irrespective of the kind of therapeutic agent employed. Season, rather than age, is suggested as the main factor in the disappearance of craniotabes. Wilson and Seldowitz (*Amer. Jour. Dis. of Childr.*, May, 1925).

Softening of the vertebral column is sufficient at times to produce kyphosis with prominent processes and other deformities, and also to contribute to the dwarfism. The growth is often arrested in rickets, though the low stature is usually due mainly to the shortness and deformity of the legs. Distortion of the female pelvis may be such as to interfere with, or actually prevent, parturition and impose Cesarean section.

The teeth usually afford distinct evidences of deficient calciophosphatic nutrition. Their eruption is delayed; they grow slowly, have saw-tooth edges, are often pitted due to loss of enamel, and soon crumble and decay. The central and lateral incisors and the first molars are the main seat of trouble in most cases.

The digestive apparatus indicates the effects of atony of the gastric and intestinal musculature. Ptosis of the

digestive system, including the liver, is common, with the "pot-belly," as previously stated. Deficient digestion and constipation normally result, while a general toxemia is often present to complicate the case.

Atony of the vascular musculature also causes general vasodilation, with recession of the peripheral blood towards the splanchnic area. This gives rise to the pallor, while the vessels of the surface, especially the veins, are dilated, as often observed on the forehead, scalp and thorax. The spleen, an internal viscus, is often distinctly enlarged.

Deficient metabolic activity entailing defective catabolism of toxic wastes, nervous symptoms due to the latter are often witnessed, *e.g.*, restlessness, convulsions, tetany, trismus, laryngismus, nystagmus. Mental dullness and backwardness at school are frequently observed among rachitic children.

Of the ductless glands, the thymus is that which gives clear indications, through X-ray examination, of either tardy evolution, atrophy, or too rapid involution. It may also be deficient owing to inadequate development. In 1903-'07 I pointed out that the thymus served, through the nucleins that it sent out through its special cells, the thymocytes, to supply the body at large with the phosphorus required for the development of the osseous and nervous systems of the growing child (see THYMUS in the article on ANIMAL EXTRACTS in Volume I). Later (1923) I showed that the active agent of these nucleins was the phospholipoid lecithin, and that the administration of the latter with parathyroid gland to promote calcium metabolism was markedly beneficial.

We have seen, however, that lecithin is only a participant in the process of metabolism—its source of heat and energy,—and that its lability as a phospholipoid is increased by the thyroparathyroid hormone.

**DIAGNOSIS.**—The laboratory findings coincide with the foregoing data. Progressive anemia is sometimes evident in untreated cases, with a blood count showing in some instances as low as 2,000,000 erythrocytes and a hemoglobin percentage of perhaps 40 per cent. The leucocytes may be increased, however, the mononuclears showing atypical shapes in severe cases. Nucleated reds are also present. In infants between the third and sixth months the blood picture may return to normal, but at other times remedial measures alone will procure this result. Any intercurrent infection may provoke a marked leucocytosis.

The urine shows, by its excess of phosphates, that the binding process with calcium is not being carried out normally.

According to Howland, rickets is invariably present when the blood concentration of phosphates is reduced from 5 mgm. to 2.5 mgm. per 100 c.c. of serum, the calcium concentration remaining at 10 mgm. This, from my viewpoint, emphasizes the functional importance of lecithin in the process, perfect equipoise between this phospholipoid and calcium in the blood being necessary to insure normal functional efficiency in all osteogenic and other vital functions. The inability of the bones and tissues to appropriate and combine these substances is shown by the fact that in rickets the stools show a marked increase of calcium and phosphorus.

As we shall see, this is due to parathyroid insufficiency, a fact which accounts also for the spasms and convulsions sometimes observed in these cases.

The X-ray findings are very helpful. There is epiphyseal enlargement. The cartilaginous extremities of long bones show an opaque line due to local density, but wherever there is sufficient decalcification, the decalcified areas appear lighter. The ends of the bones appear unusually broad and rough, with longitudinal strips of shadow indicating the uneven distribution of calcium. In the acute stage of rickets, the epiphyseal areas appear cloudy with a central mottled area of ossification. The skull may show variable areas in which the shadow appears lighter. These correspond with areas of decalcification, which entails local thinning of the skull wherever they are situated.

In *congenital osteopathy*, the absence of bone is immediately recognized in the X-ray picture. In the end group radiolucency is observed as a result of mineral absorption. The mineral is absorbed by the marrow where it comes in contact with the bone, and the bone exhibits "osteoporosis." *Rickets* shows a definite change in the epiphyseal line but not in the joint surface proper. Radiolucency may be extreme. In *scurvy* a white line just back of the epiphysis in the shaft margin is the earliest evidence. *Acute osteomyelitis* is seldom diagnosed from the X-ray plate unless it has reached the stage of abscess formation or a considerable area of bone has been attacked. The X-ray signs of *chronic osteomyelitis* are general enlargement of the bone, a more radiopaque structure, and a tendency to complete obliteration of the medullary canal. In *chronic periostitis* there is a periosteal radiolucent or radiopaque mantle surrounding the shaft. A "lace-like" appearance



of the elevated periosteum is practically an infallible X-ray sign of *syphilis*. In *chronic pulmonary periosteopathies* there is a radiopaque hair-line elevation separated from the bone by a markedly radioparent space. In secondary syphilis superperiosteal mineral deposits are readily visualized by the X-rays. *Gummata* either appear as a circumscribed periostitis, producing round nodes, or may begin in the marrow and the spongy part of the long bones. A *tuberculous* focus shows itself chiefly by a markedly increased radioparency of the structure. In *Paget's disease* there are longitudinal areas of radioparency. *Raynaud's disease* and *leprosy* give a pointing of distal phalanges. *Chondromata*, when pure, show as hyaline, radiolucent, structureless areas. *Bone tumors*, when typical, are easily recognized in the X-ray plate, although it is hard to differentiate carcinoma from sarcoma. The site and patient's age may suggest the nature of the growth. Pacini (Med. Rec., Jan. 1, 1921).

**COMPLICATIONS.**—Cases of rickets are especially liable to catarrhal disorders of the respiratory tract. The deficient endocrin organs not only lower the defensive powers of the patient, but the thoracic rôle in respiration being impaired owing to the condition of the ribs and the chest muscles, the exchanges in the lungs are inadequate. Bronchopneumonia not infrequently causes death in such cases, owing to the inability of the child adequately to combat infection.

In some areas of hypercalcification through defective distribution of calcium, or when later the treatment includes an excess of calcium over that of the phospholipoid with which the calcium phosphate is formed, the bones may become brittle and exposed to fracture. The extremities and the clavicle are especially liable to this accident.

Case of **Albers-Schönberg's disease**, with spontaneous fracture, diffuse endosteal osteosclerosis, disturbance of growth, suppurations, splenomegaly, and enlargement of lymph-nodes with myeloid metaplasia. The anemia is secondary—due to the loss of functioning bone tissue. Bernhardt (Klin. Woch., Mar. 5, 1926).

Death from rickets itself is extremely rare, but the complications it engenders, pulmonary and laryngeal, the latter including laryngospasm and convulsions, render it a dangerous disease.

**ETIOLOGY.**—The dominant lesions of rickets, those of the osseous system, have been attributed to deficiency of calcium and phosphorus, which manifest themselves through deficient formation of calcium phosphate. This, however, is not strictly correct. In the first place, deficiency of calcium may not be present. In non-rachitic infants or young children, the concentration of calcium is about 10 mgm. per 100 c.c. of serum. During active rickets, this concentration may be slightly reduced, but it is often normal and even, at times, above normal.

Conversely, there is always, in active rickets, a more or less marked deficiency of phosphorus. Thus, the concentration of inorganic phosphorus is about 5 mgm. per 100 c.c. of serum in a normal subject; this, however, is invariably reduced to  $2\frac{1}{2}$  mgm. or less in a case of rickets. Again, the administration of codliver oil causes a gradual rise of the phosphorus content, and even above normal with recovery; but relapse is attended by a fall in the serum phosphorus. This observation, recorded by Howland and Cramer in 1921, has been confirmed by other investigators.

We have seen, however, that both the urine and stools show an unusual elimination of phosphates, and, that in the stools there is an unusual elimination of calcium besides. It is evident, therefore, that they are being wasted through the absence of some binding substance. Inasmuch as cod-liver oil cures rickets, it must contain this substance. Codliver oil being a carrier of all hormones, we are brought to the conclusion that the internal secretions are the efficient agents in the curative process.

A constant increase in the phosphorus content of the blood occurs as rickets is subsiding. The curves in 4 cases showed the parallel rise in calcium and phosphorus. Salomonsen (*Norsk Mag. f. Laegev.*, July, 1925).

A clue to the nature of the glands involved is afforded by the labors of various investigators who found that thyroid and parathyroid insufficiency were factors in the pathogenesis of the disease.

The writers found a definite increase in the size of the parathyroid glands in rickets, due to actual multiplication of the component cells. Pappenheimer and Minor (*Jour. of Med. Research*, June-Sept., 1921).

From the standpoint of the post-war "late rickets" witnessed in certain underfed sections of Europe, the writers conclude that pluriglandular disturbance is nearly always present in calcium deficiency bone diseases, proper functioning of the endocrins being apparently necessary for normal calcium and phosphorus metabolism. H. Neuberger (*Zeit. f. ang. Anat.*, viii, 15, 1921).

As I have shown, the mission of these organs is to activate thermogenesis, *i.e.*, heat production in the body at large. This explains the fact that the absence of sunlight and fresh air are well known causes of the disease,

solar radiations affording normal heat, and fresh air, an ample supply of oxygen. Rickets is observed with especial frequency where sunlight is relatively scanty, in London for instance, while it is rare even among the poor who lead an open-air life. Lack of exercise also favors the development of rickets; but, as every one knows, exercise favors heat production. Briefly, adequate thermogenesis, whether of biochemical intrinsic origin, or induced by solar radiation or judicious physical exercise, will activate the curative process.

**PATHOLOGY.**—The gross anatomical changes were described when the symptoms were reviewed. The histological changes in the bones and cartilages may be summarized as a striking confusion: Irregular proliferation of hypertrophied cartilaginous cells under the periosteum, lack of uniformity in their arrangement, irregular zones of ossification, and the formation of defective bone, *i.e.*, osteoid tissue. There is a marked increase of blood-vessels, forming vascular spaces in and about the defective tissue. Whereas normal bone tissue contains about 65 per cent. of minerals, these may in rickets be reduced to 25 per cent., mainly owing to the deficiency of lime salts.

The intestinal muscularis, the heart muscle, and the skeletal muscles especially, appear inadequately developed and thin, while the spleen is more or less dilated, its pulp showing hyperplasia. The liver and heart show more or less evidence of so-called fatty degeneration.

**TREATMENT.**—The value of **cod-liver oil** in the treatment of rickets is now recognized by all clinicians and laboratory investigators. It serves

both as a prophylactic and as a curative agent by increasing, we have seen, the serum phosphorus ratio and that of the bones.

Especially does this prove true when the children are kept out-of-doors in the **sunlight**. The excessive elimination of phosphoric acid in the feces is materially reduced, indicating a greater assimilation of phosphorus by the bones. The action of codliver oil is necessarily slow, but the improvement is steady until cure is obtained. The dose is from  $\frac{1}{2}$  to 2 teaspoonfuls three times a day after meals, or less in small children.

Study of a large number of cases of rickets in a New Haven community showed that 90 per cent. of the babies had, on X-ray examination, evidences of slight rickets before they were 6 months of age. When the directions regarding **codliver oil** and **sunbaths** were followed regularly, these babies did not develop the slightest evidence of rickets; that is, the disease was controlled. In contrast to this group, the controls showed 18 per cent. of moderate or marked rickets at 10 months, 25 per cent. at 13 months, and 37 per cent. at 25 months of age. In the temperate zone rickets is a nearly universal disease among infants, whether breast fed or artificially fed. Eliot (Public Health Jour., Toronto, Mar., 1926).

The **open-air** factor is so important an adjunct to the medicinal agents used that the latter may prove useless without it. Rickets, in fact, is essentially a disease of temperate and cold climates, and is almost unknown in warm regions, where people do not shut themselves up in close rooms. It may be said to affect at least 50 per cent. of the children of industrial populations, particularly where, as in England, sunlight is relatively scarce, the average air-

space to a workman's family limited, and the children deprived of sufficient exercise in the open air.

In a statistical study of the dietetic and home conditions of over 500 rachitic children, the writer found the main etiological factors, in the order of their significance, to be improper housing, absence of facilities for open-air life, and imperfect parental care. Poverty *per se* did not seem a factor of importance. Most of the rachitic children were as suitably fed as the non-rachitic. The amount spent on rent, however, was distinctly greater in the non-rachitic than in the rachitic family. Where rachitic and non-rachitic occupied the same houses, neither the number of stairs up, the exposure, nor the ventilation seemed to affect the frequency of the disease. Quite otherwise was it, however, when the number of persons to an apartment and the general cleanliness and care of the home were considered. With the markedly rachitic children, 3.93 persons inhabited each apartment; 3.0 was the average for non-rachitic families. The average air space for markedly rachitic families was 422 cubic feet per person, for the mildly rachitic, 483 cubic feet, and for the non-rachitic families, 625 cubic feet. Nearly 50 per cent. of the rachitic children were admittedly not taken out for exercise, and only 30 per cent. seemed to be sufficiently exercised in the open air. Of the healthy non-rachitic children, 86.5 per cent. were properly exercised in the open, and only 4 per cent. did not receive the necessary airings. The seasonal incidence of the disease—spring rather than late summer or autumn—is undoubtedly due to this open air factor. The incidence of rickets would seem to be a question of economics. L. Findlay (Glasgow Med. Jour., May, 1918).

Codliver oil owes its virtues to the presence in it not only of **iodine** in organic composition, but also of other endocrin products, notably that of the

**parathyroid.** As shown by Shipley, Simonds and Parsons (1921) experimentally, codliver oil promotes the deposition of calcium in the bones while also increasing, we have seen, that of phosphorus. I have found that this function could be activated materially by the simultaneous administration of small doses of **parathyroid**,  $\frac{1}{20}$  to  $\frac{1}{10}$  grain (0.006 to 0.003 Gm.), and small doses of **thyroid**,  $\frac{1}{4}$  to  $\frac{1}{2}$  grain (0.016 to 0.032 Gm.), if stigmata of cretinism are present.

The actual deposition of inorganic phosphorus in the bones is also hastened by **sunlight**. Hess and Gutman ascertained this fact. The infants are placed in the direct sunlight for from  $\frac{1}{2}$  to several hours, the period varying according to the sun's intensity, the clemency of the weather, and the sensitiveness of the body. It is necessary that the sunlight be direct, and not transmitted through clothing or through the window glass; otherwise it loses the greater part of its curative potency, as the result of filtering out of the effective rays.

Such treatment cannot be carried out in a routine manner, but must be varied according to the condition of the babies, some of whom are far more sensitive to sunlight than others. At all times, care must be taken that the infants be kept warm. It is quite sufficient to expose the arms and legs, although it is preferable, when the temperature permits, to expose the trunk as well.

The effects of **sea air** and **sunlight** were studied by the writer for 7 years in 210 children aged from 2 to 4. Of the 42 per cent. affected with severe rickets, 68 were unable to walk. Most of them started to walk after 2 or 2½ months' treatment; others, after 7 or 8 months. About 53 per cent. had a

moderate form of the disease, and 5 per cent., a mild form. The treatment, according to the form, lasted from 3 to 12 months. **Sun baths**, mostly on the beach, were given every day, if the air temperature was not below 30° C. (86° F.). In the winter they were given from 10 to 12, for 2 hours. In the summer, the baths were given from 6 to 7 A.M., the exposure lasting only 1 hour. Besides, the children were given hot **sea-water baths**. About 200 children were cured or considerably improved. L. Jaubert (Bull. de l'Acad. de méd., June 9, 1925).

The **ultra-violet rays** and those of the **mercury vapor quartz lamp** have likewise given good results. Kramer, Casparis and Howland (1922) recommended daily exposures of from 5 to 20 minutes. Colored children responded the same as the white. The rate of recovery was about the same as with codliver oil.

**Ultra-violet radiation** causes large amounts of calcium and phosphorus to be retained in the body. Increased amounts are found in the urine, indicating an increased absorption from the intestine. Orr, Holt, Wilkins and Boone (Amer. Jour. Dis. of Childr., Oct., 1923).

The chemical substances curative of rickets—codliver oil, egg yolk, etc.—when oxidized, produce a definite blackening of photographic plates screened by quartz (the latter excluding the confusing effect of reducing vapors), while substances non-curative of rickets do not (with the exception that an effect indicating radiant energy was secured with blood). These phenomena are deemed undoubtedly due to the emission of ultra-violet radiation. Oxidation seems an important factor in the production of ultra-violet rays. Kugelmass and McQuarrie (Science, Sept. 19, 1924).

A curious fact observed by György and Gottlieb and confirmed by Pilling (Deut. med. Woch., Nov. 21, 1924) is that **eosin** given by mouth sensitizes

children to the **quartz lamp** treatment; 0.1 Gm. ( $1\frac{1}{2}$  grains) of eosin is given in 10 c.c. ( $2\frac{1}{2}$  drams) of water with the food on the day before each treatment. The total exposure required could thus be reduced from 245 to 100 minutes.

Efforts to increase the assimilation of phosphorus and calcium by the bones by means of pharmaceutical remedies have met with some degree of success. **Calcium glycerophosphate** is one of the best agents of this class. **Egg yolk** has also been lauded by competent observers. The use of the various agents found beneficial is doubtless the best course to adopt in the treatment of the disease.

**Egg yolk** found to have marked anti-rachitic properties—a feature which proved of value in connection with the tendency of bottle-fed infants to develop rickets during the winter. The procedure consists in adding the yolk of 1 raw egg to the regular feeding formulas. Egg yolk also has curative value, but less than codliver oil. A. F. Hess (Jour. Amer. Med. Assoc., July 7, 1923).

Neither woman's milk nor cow's milk will protect the growing infant from rickets. The **ultra-violet lamp**, the direct rays of the **sun**, **codliver oil** and **egg yolk** will protect. Some one of these agents should be employed daily, at least after the first month of life. A codliver oil of known value should be used. Three drams (12 c.c.) a day is not a large dose for a young infant, and in premature cases this may be supplemented with **calcium** and **phosphorus**. In cases with tetany, **calcium chloride** or **hydrochloric acid** should always be added for the immediate relief of symptoms, but the real cure must come from continued anti-rachitic treatment. Little fear need be felt as to digestion of the fat of the oil; if necessary, **egg yolk** may be substituted. J. Garland (Boston Med. and Surg. Jour., Mar. 26, 1925).

Recurrences of rickets are very frequent, especially during the second year of life. Hence, specific therapy—whether **codliver oil** or **ultra-violet rays**—should be continued after all signs and symptoms of rickets have disappeared. Again, **codliver oil** should be given not only during the first, but also during the second, winter. This is advisable particularly in infants who have had rickets and who are, therefore, susceptible to a recurrence. Hess (Amer. Jour. Dis. of Childr., Mar., 1926).

An interesting question is being tested at the present time which may ultimately prove of material help. This consists in the **irradiation of milk** for rachitic children. Thus, György (Klin. Woch., June 4, 1925) irradiated olive oil, using a **quartz lamp**. After a short time the oil smelled like codliver oil. The phenomenon did not appear if the oil had been previously boiled or if pure triolein was used. He also irradiated milk with artificial **sunlight** for 30 to 60 minutes before feeding it to children suffering from rickets. Out of 18 patients, 16 recovered within 4 to 6 weeks.

In 8 cases of active rickets the use of **irradiated milk** produced healing in every case at the end of the third week and was marked at the end of the fourth week. The chemical changes in the blood following this treatment were identical with those previously reported as following the administration of codliver oil to rachitic children, or the exposure of such children to ultra-violet rays or to sunlight. Irradiated milk feeding induces a marked retention of both calcium and phosphorus. Kramer (Amer. Jour. Dis. of Childr., Aug., 1925).

Bone deformities require special attention. To forestall them or prevent their occurrence and correct them the child should be kept off its

**feet and splints** or apparatus applied. Splints of the simplest character, such as those made of pasteboard and bandaged on, are of considerable service. Simple supports for the back are also valuable. If the disease is marked, deformities will occur even though the child does not stand on its feet. Wimberger (Zeit. f. Kinderheilk., Sept. 28, 1925) found that **massage** of the legs twice a day helped in the treatment of rickets in infants taking codliver oil, but not in others.

Old rachitic deformities in children are treated by the writer without operation by temporarily **softening the bones** by induction of an acidosis, then bending them to the proper shape and applying a **cast**. The child is given daily 0.15 to 0.25 Gm. (2½ to 4 grains) of **ammonium chloride** per kilo. of body weight, preferably with 12 parts of sugar, in 20 parts of distilled water. At the same time **venous stasis** is induced in the affected extremities for about 20 hours daily. The bones elsewhere are probably slightly softened and the child is therefore kept in bed. In 8 to 12 days or somewhat longer the deformed bones are so softened that they can be bent by 30 to 40° with but slight force. The cast having been applied, a rehardening process which occupies 4 to 6 weeks is gone through, consisting of the use of the **ultra-violet rays, phosphorus, codliver oil, fresh vegetables, fruits** and a little **calcium lactate**.

The method is not available in children over 6 years of age nor in adults, and is contraindicated by renal disease. C. R. H. Rabl (Munch. med. Woch., Apr. 11, 1924).

The writer applied Rabl's method with success in 13 children below the age of 3 years; it failed in 2 boys aged 4 and 7. The bones were softened within 12 days. He considers the method a great improvement over the earlier non-operative procedure requiring months of immobilization. J. Elsner (Zeit. f. Chir., Dec. 6, 1924).

## OSTEOMALACIA.

**SYNONYM.**—Mollities ossium.

**DEFINITION.**—Osteomalacia, or softening of the bones, is due to deficiency of substances required for osseous tissue to preserve its functional integrity. These substances consist mainly of phospholipoids and calcium for the formation of calcium phosphate and of the thyroparathyroid hormones which sustain calcium metabolism in this process. (Author's definition.)

An important relationship between osteomalacia and the parathyroids, which endocrinologists have long urged as factors in calcium metabolism, is again illustrated by the following cases: Schlagenhauser (Wiener klin. Woch., xxviii, 1362, 1915) reported 2 cases of tumors of the parathyroids. One was in a 43-year old man who had had osteomalacia for 5 years, while the base of the skull showed changes resembling those of osteitis fibrosa. The left lower parathyroid was of the size of a plum; histologically it was almost normal. The other patient was a 62-year-old woman who had had osteomalacia for 15 years. The right lower parathyroid was of the size of an almond. Histologically it, too, was almost normal. In the discussion Maresch said that he had performed autopsies in 23 cases of osteomalacia. In 10 cases in women from 58 to 82, the parathyroids were only moderately enlarged, or had merely not atrophied as had the other parenchymatous organs, thus showing a relative enlargement; but there was no pronounced parathyroid tumor in any of these cases. Bauer recalled that osteomalacia is frequently associated with tetany. Tetany being a sign of parathyroid insufficiency, adenomatous parathyroids might be defective in function; in that case a further removal of parathyroid tissue would be injurious. In a case of osteomalacia observed by Bull and Harbitz (Norsk Mag. f. Laegevid., lxxvi, 417, 1915), a tumor as large as a walnut was found in the left lower parathyroid gland. They recall that similar tumors have been found in other cases of osteomalacia, but have also sometimes been found in cases without osteo-

malacia. Harbitz had also observed a case in which there was a tumor in all 4 parathyroids in a man of 75, with paralysis agitans, in which nothing suggested osteomalacia.

All these cases, from my viewpoint, point to enlargement of the parathyroids as an inadequate effort to compensate for their insufficiency. C. E. DE M. S.

**SYMPTOMS.**—The initial manifestations of osteomalacia are recognized with difficulty. Dull "rheumatic pains" or "neuralgia" about the sacral region, back, thorax or joints, aggravated by motion, remaining long in one position, or pressure, usually suggest some disorder, metabolic or nervous, other than osteomalacia, particularly in view of the fact that girdle pains are sometimes complained of, while hyperexcitability of the muscles is almost always present.

In a series of 28 cases, some in men, the writer noted, as initial symptoms, constant tenderness at the symphysis, along the pubic arch, especially on its inner aspect, and at the spinous processes of the 3d to the 8th thoracic vertebrae and the sternum. Sitting was frequently painful on account of the sensitiveness of the tuberosities of the ischia. Buckhardt-Socin (*Arch. f. Gyn.*, cxxi, 61, 1923).

General myasthenia and stiffness of the muscles or, conversely, spasmodic movements leading up in some instances to true tetany, positive Chvostek's sign, increased patellar reflex, intention tremor and paresthesia, all of which I attribute to toxic intermediate wastes, tend also to suggest some nervous disorder.

In due time, however, the progressive softening of the bones entails deformities, which become especially apparent when the patient is examined unclothed. The spinal column and the pelvis usually show the first suggestive deformities.

The height of the patient may be found decreased, more or less lordosis or kyphosis being observed to account for it. The pelvis shows a greater or less decrease in its diameters, causing the patient to assume a waddling gait. Bending forward of the sternum and approximation of the hips towards the thorax are seen. The long bones may also become distorted and suffer fracture more or less frequently, due to muscular traction, often spastic, as we have seen.

The functions of the viscera seem but little influenced, including the gastrointestinal and procreative. In cases due to pregnancy, however, the bone lesions are purely maternal, the fetal skeletal showing none, as a rule.

The blood presents the characteristics of a deficiency disease. There is, in fact, a low  $\text{CO}_2$  combining power of the blood, lowered sodium and chloride values with an increased ammonia coefficient, and acetone in the urine, *i.e.*, a starvation acidosis. The blood cells may show evidences of chloranemia, but apart from the chemical changes just outlined, no characteristic features have been discerned.

In 2 cases of osteomalacia in children observed by the writers, studies of the mineral metabolism showed a lowered retention of calcium, magnesium and phosphorus. In 1 of the little patients the calcium loss reached a negative balance. That a hereditary factor was present is suggested by the fact that the mother of one of the patients had a history of 6 fractures, even though heredity had not so far been clearly traced in the disease. Dwyer and Eckelberry (*Amer. Jour. Dis. of Childr.*, May, 1926).

The skin appears flabby, relaxed and sallow. Edema is more or less marked, particularly over the affected extremities. Tachycardia, dyspnea, fever and

sweating, with pulmonary disorders, bronchitis or edema, bedsores, etc., are the usual precursors of a fatal ending by cachexia.

The duration of the disease varies from 1 year or less to a decade or more. Pregnancy and menstruation tend to aggravate the disease. Rarely, however, spontaneous recovery occurs.

Case of extreme osteomalacia from early infancy in a girl aged 17 at the time of the report. The softness of the bones had caused deformity of the thorax, spine and limbs. Deranged metabolism, chiefly of calcium and phosphoric acid, was found to prevail. Spontaneous fractures were frequent; but contrary to what is observed usually in osteomalacia, consolidation proceeded normally. Attacks of spontaneous pains occurred every winter, lasting 2 or 3 months. Localization of the pain in the limbs seems to be characteristic for osteomalacia in children. The X-rays showed the presence of calculi in both kidneys and bladder, revealed clinically only by pyuria. J. Dereux (*Presse méd.*, July 3, 1926).

### ETIOLOGY AND PATHOLOGY.

—A close kinship between osteomalacia and rickets has increasingly asserted itself in recent years. Formerly, pregnancy was believed to be the main cause of the disease, but its widespread occurrence in Central Europe coincident with a lack of certain foods showed clearly that it was a deficiency disease in which fat-soluble vitamins in particular were the main absentees, with phosphorus and calcium deficiency as important features of the morbid process.

Out of 75 patients with osteomalacia examined by the writer, the disease began during pregnancy in 31 per cent. and in 30 per cent. during the nursing period; 80 per cent. were worse in winter and spring; in 39 per cent. the teeth were painful and loose. Out of

a total of 130 children born to osteomalacic mothers, only 54 are living. There was also a familial tendency. The survey showed that osteomalacia resembles rickets in that it attacks people living in poor hygienic surroundings, lacking sunshine, and taking insufficient exercise. F. J. Wampler (*China Med. Jour.*, May, 1924).

The prevalence of this disease among men as well as women during the World War and during the famines in China has indicated that it must be placed among the deficiency diseases. The writer found the serum of such cases deficient in calcium and in some instances, in phosphorus, according to the severity of the disease and its duration. Adequate food brought relief. Miles and Feng (*Jour. of Exper. Med.*, Jan., 1925).

As in rickets, the lack of sunlight, out-of-door life and physical exercise likewise plays a marked etiological rôle in osteomalacia, since it occurs as well among the wealthy in whom the diet is ample, when these factors are not provided.

The mere addition of carbohydrates to the diet caused little improvement in the food deprivation cases observed in Vienna, but recovery occurred upon administration of the following agents, the efficacy of which was as in the order given: **Codliver oil, butter, oleo-margarine** containing 80 per cent. of animal fat, and **olive oil**. The effects thus corresponded roughly to the content of fat-soluble vitamin A. The relationship of this "hunger osteomalacia" to the osteomalacia of pregnancy is uncertain. Reichel (*Munch. med. Woch.*, Sept. 30, 1921).

Practically all Kashmir women who have borne children are affected in some degree with osteomalacia. They live in the open air on large freight boats, work hard and eat with the men. They are too poor to cook their food much, and eat raw cucumbers, tomatoes, etc., with their rice. The worst cases, however, occur in the houses of the wealthy, who keep their



women in seclusion, and among those of the poorer classes who do the same. Many deaths of both mother and child take place in childbirth. Vaughan (Brit. Med. Jour., Mar. 6, 1926).

Prolonged lactation is another cause of osteomalacia, especially if the pregnancies, which themselves increase the liability to the disease by using up the maternal phospholipoids to develop the fetus, are multiple. A suggestive peculiarity of such women is their craving for earthy substances.

The belief that the disease only occurred in women was forever dispelled by the World War, which showed the marked etiological influence of starvation in both sexes. The form due to pregnancy, however, seems more frequent in young subjects. It occasionally follows osseous traumatism, through lowering of the assimilative vitality of the bones.

Exophthalmic goiter has been found to cause osteomalacia in some cases, owing, from my viewpoint, to the active consumption in this disease of the tissue phospholipoid, including that of the bones. A connection has also been observed between the parathyroids and calcium metabolism, the glandules showing hyperplasia indicative of compensative overactivity in many instances, as exemplified by cases cited under DEFINITION at the beginning of this section. The anterior lobe of the pituitary has also been suggested as a cause, but on unsatisfactory evidence. This indicates the participation of the other endocrin glands in the morbid process, the thyroid and adrenals in particular.

As evidence of polyglandular endocrin insufficiency in osteomalacia the author enumerates the following symptoms: Osseous gracility, hyperplasia of the bone marrow, decalcification, sensi-

tiveness of the periosteum, which is markedly influenced by exhibition of adrenalin; muscular dystrophies; psychic disturbances; increased reflexes, spasms, tremor, pyrexia, hyperidrosis, paresthesia, disturbances of metabolism, and changes in hematopoiesis. As to lesions of the endocrin organs, insufficiency of the hypophysis and supra-renals has been met with as evidenced by the favorable results from exhibition of extracts of these glands. The hyperfunction of the genital glands is demonstrated by the influence of castration. The parathyroids are often hypertrophied, but this is common in all kinds of calciprive diseases. Naegeli (Munch. med. Woch., May 28, 1918).

The histological changes in the bone tissue are variable, but decalcification seems to be the earliest phenomenon observed. Hence the softness, which has caused the disease to be termed "mollities ossium," the bones being spongy, pliable and readily cut. In the long bones the medullary cavity is enlarged and, as the disease progresses, the periosteum is stripped off, leaving a number of openings, which exude a yellow or reddish serous fluid. The size of the bone is usually reduced and its shape more or less altered, while the marrow itself may be changed in color and become lymphoid. The density of the bones is often reduced over one-half, sufficiently so, in some instances, to permit the passage of X-rays so that the bone is hardly visible. Hence the fact that these rays are of but limited value in the diagnosis of this disease.

**TREATMENT.**—The treatment of osteomalacia is in its general lines similar to that for rickets, *viz.*, **cod-liver oil, sunlight, out-of-door life** and, where possible, **physical exercise**. Although of no particular value in rickets, **phosphorus** often proves very

effective in osteomalacia. An excellent method of administration is that of Kasminski. He first gives 2 teaspoonfuls a day of a mixture containing  $\frac{1}{3}$  grain (0.021 Gm.) of **phosphorus** and 3 ounces (90 c.c.) of **codliver oil**. He then gradually increases the daily dose until 6 teaspoonfuls are taken daily, the patient being closely watched. The mouth must be kept scrupulously clean. The treatment continues for 4 to 14 months. Curschmann found phosphorus efficient when used energetically and for a long time in senile osteomalacia.

In a girl aged 17, in whom the disease had started at the age of 10, vagotonia was manifest. While organotherapy proved ineffective, administration of **phosphorus** caused a marked amelioration. Urechia and Bodea (Bull. Soc. méd. des hôp. de Paris, Mar. 27, 1925).

I have found **lecithin** in  $\frac{1}{2}$  to 3 grain (0.03 to 0.2 Gm.) doses, according to the age, 3 times a day before meals, efficient, the phosphorus of this lipoid being the beneficial factor, especially so in view of the fact that as such it is readily assimilated by all tissues, including the bones. **Desiccated suprarenal** in 2 grain (0.13 Gm.) doses after each meal is a markedly helpful adjunct, the cortex supplying lecithin and the medulla adrenoxin or adrenalin, the oxidizing principle of the adrenal substance.

Case in a multipara of 38 in which no treatment, not even oöphorectomy, produced any lasting effect until **adrenalin** was given; the third injection of 1 c.c. (15 minims) was followed by marked improvement. Koltonski (Monatschr. f. Geb. u. Gynäk., Oct., 1920).

**Thymus grafting** has been resorted to with success. As is well known, the nucleins of this gland, if removed

from young subjects, are rich in phosphorus, embodied in its nucleins.

The writer resorted to **thymus grafting** in a case of osteomalacia which had begun during the patient's 8th pregnancy and had progressed for 2 years. The grafts, obtained from the thymus of a female newborn infant, were implanted in the abdominal wall. The results were as good as those obtained from ovariectomy. The intense pains disappeared on the 4th day after the operation, and on the 10th day the patient was able to walk. The writer holds, after an experimental research, that osteomalacia is due to deficient activity of the thymus. There had been no recurrence during the 3 or 4 months to date. Scipiadès (Zent. f. Gynäk., Aug. 30, 1924).

Cure has been said to follow **oöphorectomy** in 87 per cent. of cases in which the operation was resorted to, the explanation of Fehling, Curschmann and others being that the ovaries are overactive. In the light of my own labors, however, this explanation is incorrect, the true one being that the ovaries drain the body of its phospholipoids, particularly that of the adrenals, to form their interstitial cells. Removal of the ovaries, then, by arresting this drain, liberates a sufficient amount of phosphorus in organic combination to supply the osseous system with a greater proportion of this element. The simultaneous administration of **codliver oil** and **phosphorus** could not in these conditions but hasten the cure. **Ovarian gland** is also said to be effective, owing, from my viewpoint, to the lecithin its interstitial cells contain.

Three years after the onset of the disease in a secundipara aged 38, the writer removed the ovaries. Twelve months later the patient was greatly improved in all respects. Hellier (Brit. Med. Jour., Oct. 16, 1920).

The writer describes at length 2 cases in which recovery followed the administration of **ovarian extract**. Gentili (Rif. med., Jan. 30, 1922).

The operation might, in the future, be rendered unnecessary by the use of **X-rays** in sufficient dosage to arrest the ovarian functions.

Four cases treated by **X-ray exposures** of the ovaries, with favorable results. Some cases can be cured without raying the ovaries sufficiently to arrest menstruation; in others it may be necessary to arrest the ovarian function. Kalman (Orvosi hetil., June 18, 1922).

The administration of **thyroid gland** in small doses and of **parathyroid** in  $\frac{1}{10}$  grain (0.006 Gm.) doses is indicated to insure adequate combination of the phospholipoid with the calcium. Some cases are aided by the simultaneous administration of **lime water** or **calcium lactate**, the latter in 5 grain (0.3 Gm.) doses 3 times a day. This applies to cases in which the intake of calcium with food, vegetables, milk, etc., has been deficient.

### **FRAGILITAS OSSIUM.**

**SYNONYM.**—Osteopsathyrosis.

**DEFINITION.**—Fragilitas ossium is a deficiency disease, often hereditary, characterized by abnormal brittleness of the bones, due mainly to a deficient intake of the phospholipoids which combine with calcium in the formation of osseous tissue. (Author's definition.)

**SYMPTOMS.**—This disorder is characterized by a liability to fractures under the influence of slight traumatism, as in falls, or occasionally without assignable cause. Successive fractures of many bones may thus occur; but, rapid recovery ensuing, the only result is gradually increasing deformity of the patient as a whole

and the gradual loss of ambulatory power.

The number of fractures which these patients sustain sometimes exceeds 100. The long bones, the femur especially, are those usually affected, the shoulder blades, skull, pelvis, and spinal column being those least often fractured. A sudden pain may occur at the seat of fracture. As a rule, a slight fall or twist may cause it, but it may occur while the patient is in bed, owing to muscular contraction on changing position or turning.

The fractures may occur during intra-uterine life or in infancy. In the newborn many may sometimes be counted, along with combinations of old fractures united or partly united and of loose, recent fractures. Curiously, however, union is usually rapid.

The diagnosis of such cases is readily made, but the X-rays make it possible to ascertain the nature of the disorder by demonstrating, in some instances, the presence of previous fractures. The condition may easily be mistaken for exophthalmic goiter, as in the following instance, in reality a case of the latter disease:

In a case of fragilitas ossium (idiopathic osteopsathyrosis) observed in a negro of 38 years, tests showed that the calcium and phosphorus of the blood plasma and bone, and likewise the magnesium of the bone, were normal. The basal metabolism was increased, with marked exophthalmos, a palpable thyroid, immature genitalia, shallow pituitary fossa, slight tachycardia, blue sclerae and impaired hearing. No history of syphilitic infection or bone disease in the family could be obtained. Amputation of a leg became necessary, and the tibia showed a broken and thinned cortex with dis-

tended Haversian canals and increased bone resorption. G. W. Wagoner (Ann. of Surg., July, 1924).

Had the above been a true case of fragilitas ossium, the calcium would at least have been found reduced, as in the following typical case in which the organically bound calcium was *nil*:—

In a girl of 4 months with multiple fractures of long bones there was 25 mgm. of ionized calcium in 100 c.c. of cerebrospinal fluid. No organically bound calcium, however, was found. After 22 irradiations with a **quartz lamp**, the ionized calcium was 28 mgm. and the total 39 mgm. No fractures occurred after this treatment. Ferri (Pediatria, Jan. 1, 1925).

Blue sclerotics were noted in 3 cases by Burrows in 1911, this phenomenon being present in 13 members of the patient's family, 9 of whom gave a history of having had fractures, multiple in the majority of instances.

**ETIOLOGY.**—This feature of the problem has remained obscure. While most cases of fragilitas ossium show clear evidences of heredity, and that the disease is a familial one, various members of the same family being more or less subject to it, the cause appears to be, from my viewpoint, a deficiency of the phospholipoid lecithin, which, with calcium, serves to build up the osseous calcium phosphate. As the adrenal cortex is the main source of lecithin, with the thymus as a potent adjunct during development, while the thyroid and parathyroids stimulate the activity of the lecithin, fragilitas ossium appears to be mainly due to insufficiency of these various endocrins. What empirical use has been made of organotherapy serves further to sustain this personal interpretation.

While most cases may be traced to hereditary influence, the disease is

observed in infancy, childhood and adult life. Most cases occur in the young, during the period of skeletal development, and but rarely after the thirtieth year. In old age, in fact, the disturbance is often termed osteoporosis, owing to the porous condition of the cancellous tissue of the shaft, the latter being usually more slender than normal.

Fragilitas ossium is also an occasional sequence of exophthalmic goiter, as in the case reported by Wagoner, quoted under SYMPTOMS, the condition being then due to excessive catabolism of the osseous lecithin. It is also observed in various deficiency diseases, such as scurvy and rickets, in which the osseous pabula are inadequately supplied by the food; in various nervous diseases; in bone traumas, and in diseases in which the nutrition of the bones is lowered, or the supply of one or more of the vitamins is inadequate.

**TREATMENT.**—In fragilitas ossium the condition of the bones is the opposite of that considered under the preceding heading, mollities ossium. Whereas in the latter the bones are soft and yielding, bending readily, in fragilitas ossium they are brittle, and break as would slender pieces of chalk. Hence the fact that **codliver oil** and the **glycerophosphates** have been found curative, while **thyroid** and **parathyroid** are indicated in doses suitable to the patient's age. **Phosphorus** may be added to codliver oil with profit. **Thyroid grafts** have been found efficacious where degeneration of the transplants had not occurred.

While the blood calcium is not reduced in fragilitas ossium, and the bones are plentifully supplied with this element in most instances, the

fact remains that in the curative process, new calcium phosphate is formed. It is, therefore, advisable to administer calcium with the other agents indicated—**lime water** in infants and **calcium lactate**, or better, **calcium phosphate**, in older children and adults.

### OSTEITIS AND PERIOSTITIS.

**DEFINITION.**—Inflammation of bone (osteitis) and of the periosteum, its fibrous investing membrane (periostitis), due either to traumatism, extension of inflammation from other regions, constitutional diseases, such as tuberculosis and syphilis; various febrile infections, such as typhoid fever and influenza, and certain poisons, such as mercury and phosphorus.

**SYMPTOMS.**—While in certain forms, such as that due to tuberculous infection, the onset and course of osteitis *per se* are insidious and slow, the disorder giving rise at first to but few symptoms except perhaps slight swelling, local discomfort and some sensitiveness to pressure, marked pain and constitutional disturbance may become manifest when the peripheral or surrounding parts have become affected. This applies especially to the periosteum, which is practically always involved in the morbid process. Hence the advisability of considering both the osseous and periosteal inflammatory symptoms in the present connection.

**PERIOSTITIS.**—When the periosteum is the seat of an acute inflammation following an injury, there is a localized swelling, redness, heat, and pain—which is usually worse at night. The tenderness is exquisite, and the use of the part is much interfered with. A spindle-shaped enlargement can often be felt, due to

thickening of and effusion into the periosteum, sometimes with detachment of it from the underlying bone. A collection of blood may form between the detached periosteum and the bone beneath. This collection is liable to be mistaken for pus, but the surface is usually not so red as when pus is present. The anterior surface of the tibia, being most exposed, is the most frequent site of the trouble, but the clavicle and other bones may also be affected. When no infection occurs from purulent microorganisms, suppuration may not occur. If, however, the acute form supervenes during some infectious disease, suppuration is apt to take place, and constitutional symptoms—severe in proportion to the extent of the inflammation—ensue. Even should the involved area not be extensive, suppuration is apt to be prolonged and extremely obstinate, in some cases causing death from exhaustion.

Diffuse periostitis is a serious variety in which the inflammation spreads rapidly, sometimes including the periosteum of the entire shaft. It may reach the epiphyses and the joints and extend deeply into the osseous tissues, perhaps as far as the medulla. Pyemia sometimes appears in these cases and generally ends fatally, although in children recovery may ensue even after metastatic abscesses have shown themselves in several parts of the body.

Periostitis frequently follows injuries; it may also arise spontaneously as a sequel to variola, typhoid fever, scarlet fever, and other infectious diseases. The complication, as a rule, however, only occurs at the end of convalescence. After typhoid fever

the tibia is usually implicated, and the jaws after scarlatina and measles. Periostitis more frequently occurs as a complication in the young than in the adult, and may make its appearance long after all symptoms of the original infective disease have subsided and the patient is apparently well.

It may be primary, or secondary as the result of inflammation of the underlying bone or the medulla. In syphilitic and tuberculous subjects a local periostitis may arise without any discoverable traumatic cause. It is probable, however, that in many of these apparently idiopathic cases there has been a previous, unnoticed trauma, of a degree which would not have affected a healthy periosteum. (G. G. Davis.)

#### ETIOLOGY AND PATHOLOGY.

—The dominant causes of osteitis were enumerated under DEFINITION. After a bone injury, as in the case of fracture, blood and serum are effused at the affected spot. The periosteum and surrounding parts become infiltrated with leucocytes. From the periosteum and the adjacent bone stellate cells are proliferated. The effusion in which they occur becomes first hardened and striated, and lime salts are deposited. The stellate cells become full-fledged osteoblasts, which finally develop into bony tissue. In cases resulting from simple injury the natural state of affairs is soon re-established. Occasionally an anomalous course is pursued. The bone may become uniformly increased in all dimensions, constituting a true *hyperostosis*, or, if the density is increased as well as the thickness, an *osteosclerosis*.

In this disorder the bones of the head

are most often affected, and the disease may last many years. When osteitis attacks the bones of the face a very peculiar appearance results, to which Virchow has given the name *leontiasis ossium*. The disease begins in youth in otherwise apparently healthy persons and lasts many years.



Syphilitic periostitis in a child of 14 years.  
(Fischer).

The histological changes in the periosteum proper consist in a temporary thickening of the periosteum, followed by rapid cell-proliferation and the formation of inflammatory lymph. When pus forms on bones which are subcutaneous, as the tibia or clavicle, if the process is acute, the skin and overlying soft parts may

soon be perforated and a discharging sinus is formed. The parts may remain thickened or hardened (sclerosed), though the underlying bone, through defective nutrition, becomes soft. Especially in chronic processes, healing may occur without external suppuration, and then the surface remains rough and uneven, due to the bony deposit from the diseased periosteum. Diffuse inflammation so reduces the osseous nutrition sometimes as to cause death of bony areas: caries, necrosis (see *OSTEOMYELITIS*, farther on in the present article).

**TREATMENT.**—In simple osteitis, the preliminary measures indicated do not differ essentially from those employed in the treatment of inflammation of the soft tissues.

If the case be recent and acute, the patient should be put to bed and the limb raised and placed in a splint, with cold applied to obtund the pain. **Morphine** may, however, become necessary. If there is no superficial lesion counterirritation by means of **iodine** is in order. **Blue ointment** may prove useful.

An attempt to localize the morbid process in the bone proper should be made. Prompt and radical surgical measures may do so, but if it is quiescent it need not be disturbed until a sequestrum becomes detached within the cavity. Then the latter may be freely opened, the sequestrum removed along with what granulations are present, and the cavity swabbed with **phenol**. Removal of the infected material is usually followed by healing and the reproduction of bone.

The introduction of **bismuth paste** into the sinus, advocated by Beck, of Chicago, has given good results. Yet,

the use of this measure requires great care to prevent poisoning (see *BISMUTH*, this Volume) by the arsenic which bismuth sometimes contains or through absorption of bismuth into the tissues. A third source of possible intoxication is the conversion of bismuth subnitrate into a nitrite.

Injections of **iodoform** and **spermaceti wax** after a preliminary **curettage** have been advocated in certain cases, especially tuberculous, and are warranted when the bone is not likely to be too much weakened by the removal of all the diseased tissues. Allowing the soft parts to fall in over the deficiency, *i.e.*, **plastic obturation**, has also been advocated.

Where a deep recess in a bone has been left through removal of bone tissue for osteitis, the writer makes superior and inferior transverse skin incisions above and below the site of disease. The resulting lateral flaps are mobilized for some distance and then drawn together down into the center of the bone defect. Three to 6 radiating incisions may be made, to permit better coaptation of the skin flaps over the defect. Dressings being insufficient to hold the flaps in place, the author, after retracting the flaps laterally, makes holes with an awl through the bone and passes through them bronze wire, which issues near the bottom of the groove in the bone and holds the margins of the flaps down in place. Usually 2 or 3 bronze sutures are used for each flap. At both ends of each bronze wire a small packet of gauze is placed to prevent injury to the skin. After having been fastened with the wire, the flaps are united at their margins by a few sutures. The bronze sutures are kept under observation on and after the third day, and are removed whenever the pressure at the point of fixation is seen to be threatening the vitality of the flap. A number of cases of osteitis after war wounds

were treated successfully by this procedure. D. Thevenard (*Presse méd.*, Oct. 7, 1918).

Nine patients with chronic osteitis of the mastoid or temporal region consecutive to middle ear disease were cured under **carbon arc light** exposures. The treatment occupied up to 9 months in some. The benefit was equally pronounced in the tuberculous and the apparently non-tuberculous cases running a protracted course. O. Strandberg (*Hospitalstidende*, May 1, 1918).

A bone should never be resected for a single focus of fibrous osteitis. In a case in a girl of 10, roentgenograms showed bone tissue gradually filling up the cavity of the solitary cyst after curetting. Eleven months later not a trace of the cavity remained. Lotsch (*Deut. med. Woch.*, June 3, 1920).

As regards periostitis, many cases are kept active by the continued irritation of the part through lack of rest. All sorts of ointments and medications are often applied, yet the most important element of treatment—**rest**—is neglected. The muscles being inserted in the periosteum, their contraction disturbs the latter, and the periostitis cannot subside. The first indication, therefore, is to order the patient off his feet if the lower extremity is involved or thoroughly immobilize the part if in the upper extremity. Not only should this be done, but all movements of the affected member should be prevented by encasing the limb in a **plaster-of-Paris dressing** or securely bandaging it to a **splint**. Not only should the part immediately involved be splinted, but also the regions, especially the joints, above and below, so as to prevent the adjacent muscles from disturbing it. If the foot is the seat of trouble, it should always be kept at rest and preferably **elevated** when the lower extremity is involved, and the

hand when the upper extremity is affected.

Local depletion is also efficient. Multiple **punctures** of the swelling may be made with a slender tenotome or cataract knife. Instead of these punctures, a **subcutaneous incision** may be made through the swollen tissues down to the bone. Such an incision gave almost immediate relief in a periostitis affecting the femur which had been causing pain and total disability for several weeks. This puncture or incision should be done with proper antiseptic precautions.

In chronic, troublesome cases in which the upper layers of bone are involved, making an **incision** down to the bone and then **boring** several small holes into it—the aim being to **relieve tension**—and finally putting the limb in **plaster of Paris**, has been followed by the most gratifying results. To wait for the formation of pus in these cases before operating is in the highest degree undesirable, as an earlier boring of the bone cuts short the disease at once and prevents the occurrence of suppuration.

In cases of acute infection involving areas of considerable extent and accompanied with high fever and other evidences of constitutional sepsis, **free incisions** down to the bone, splitting the periosteum wide open, under anesthesia, are to be made at once. (Davis.)

After a brief febrile disease diagnosed as influenza, exploratory puncture in a circumscribed bone focus near the trochanter disclosed virulent paratyphoid B bacilli. The roentgenograms suggested either a sarcoma, except that the cavity showed uniformly clear with sharp outlines, a cyst, or a focus of osteomyelitis. **Aspiration** of 20 c.c. of blood and pus through a lumbar-puncture needle caused the process promptly to retrogress. The



femur seemed to be quite normal 8 months later. **Light traction** had been applied to the thigh after the evacuation. Ceccarelli (Archivio ital. di chir., May, 1925).

### **OSTEITIS DEFORMANS; PAGET'S DISEASE.**

**DEFINITION.**—Osteitis deformans is a localized thickening in one or more bones, due to irregular deposition in them of the chemical components of osseous tissue, notably the phospholipoid lecithin and calcium, with deficiency of the endocrin products, those of the thyroid and parathyroid glands in particular, which insure the normal combination of these components. The general symptoms observed are identical concomitants of the disturbances of metabolism to which osteitis deformans is due. (Author's definition.)

**SYMPTOMS.**—So-called "rheumatic" pains are usually complained of, with progressive ambulatory difficulty, increasing awkwardness of the arms, and general myasthenia. After a time, which varies greatly in the different cases, the patient may find that his hat causes an uncomfortable pressure, and he finds it necessary to use increasingly large sizes. The skull has actually become larger. In rare instances it grows symmetrically, in the majority laterally and irregularly, the dominant projection or *bosse* being located either atop the head or at the forehead, the latter projecting prominently beyond the deformed head. While headache is sometimes absent, it may develop and become severe, often with increasing deafness which, in some patients, may become absolute. The eyes remain normal, though rarely, cataract and edema of the lids, and perhaps of the face, have been observed.

The skull, however, is not the only seat of pathological alteration. The patient finds, after a time, that his legs are becoming increasingly bowed, all the bones, in particular the femur, tibia and fibula, yielding to the weight of the body, according to some authors, and to traction of the muscles upon softened bone tissues, according to others. That the latter view is sound is suggested by the fact that the arms and clavicles may also become bent. Thickening also occurs in the long bones, due to the same conditions as cause the skull to thicken and bulge. But one bone may be affected to begin with; the morbid process may then become generalized and involve every bone in the body. Locomotion becomes more or less impaired and spontaneous fractures may occur, which, however, tend to unite.

The body in general, owing to softening of the vertebræ, becomes shorter by several inches in some instances, the ribs being approximated and giving the chest an appearance of increased expansion though more or less fixed, suggesting the presence of emphysema. Percussion, in fact, elicits hyperresonance in most cases. The heart may be slightly enlarged and the arteries sclerotic and tortuous.

Laboratory examinations show no suggestive changes which could be attributed to the disease, the blood, urine, and blood chemical findings approximating normal. The Wassermann test is also negative in practically all cases. The blood-pressure approximates normal unless a renal concomitant disorder be present.

Analysis of a series of 20 hospital cases led to the following conclusions: Most of the patients with advanced osteitis deformans, both male and

female, were past 50 years of age. A certain degree of deafness existed in all. Most patients showed marked arteriosclerosis. Almost all gave negative Wassermanns. Nearly all showed involvement of other bones besides the skull. All gave normal or nearly normal blood sugar, blood urea, and blood uric acid, except where kidney disease also existed. Nearly all the patients had had, off and on, rheumatic pains many years before the true picture of Paget's disease appeared. H. I. Goldstein (Med. Times, Aug., 1926).

Of itself osteitis deformans rarely causes death. It runs a very chronic course, lasting perhaps 10 to 20 years. Death is due to some intercurrent disease.

**ETIOLOGY.**—Osteitis deformans occurs somewhat more frequently in males than in females. Although it is occasionally observed in young subjects, it is encountered as a rule in individuals over 40 years of age. It does not appear to be hereditary, and shows no causal connection with rheumatism, gout, syphilis or any bacterial disease. Nor is it *per se* attributable to any bacterial infection. Injury to the head and severe falls had occurred in several of the cases reported.

The bulk of opinion at the present time favors the view that the disease is due to some endocrin disorder, the thyroid gland having been found atrophied (compensative, probably) in two, while the adrenals and pituitary appeared normal. In 1 case, at least, the parathyroid glandules could not be found.

**PATHOLOGY.**—The bone deformities are due to a transformation process in which the bone first becomes softened and vascular, then thickens greatly, beginning with the bone-marrow, and is filled with white

and giant cells. There is formed a considerable quantity of new bone, but it is deficient in structure and lacking in calcification.

The thickening assumes marked proportions, often to two or three times the normal size. The new bone formation occurs on the outer lamella, acquiring, in some instances, an ivory-like density in prolonged cases. In some instances, however, the bones never reach this stage, and remain soft and friable, opportunities for spontaneous fracture being thus afforded.

Transformation of the abnormal bone into malignant growths has been observed, endothelioma, sarcoma, enchondroma in the bone itself, *i.e.*, osteosarcoma, or elsewhere, having been reported.

**TREATMENT.**—Measures calculated to alleviate the patient's suffering are eminently in order, **anodynes** and **soporifics** especially. Considerable comfort can be afforded from the use of a proper **supporting apparatus**. Improvement is said to have followed the use of **potassium iodide** and **thyroid gland**, the latter being well known to influence markedly calcium metabolism and general nutrition.

The work of Collip on parathyroid-ectomized dogs having shown that extract of **parathyroid gland** raised the calcium content of the blood, Bassler tried this substance in a case, with satisfactory results, after all other resources in this country and Great Britain had proven useless. This treatment, from my viewpoint, started the bone-building process in the right direction by acting as metabolic binder for the phospholipoid lecithin and calcium.

Case of typical Paget's disease in a man of 60 years who, on January 11, 1926, was just able to stand with 2 canes and move about very slowly and carefully. None of the measures tried having benefited him, he was given **parathyroid tablets**,  $\frac{1}{10}$  grain (0.006 Gm.), one after each meal, thrice daily. Within 1 week he felt much stronger, seemed to walk better and moved about with greater assurance. March 10, after taking the parathyroid about 8 weeks, he walked 2 miles and more each day, using a cane only when out. A. Bassler (Jour. Amer. Med. Assoc., July 10, 1926).

### OSTEITIS FIBROSA CYSTICA.

This type of osteitis must be clearly differentiated from the osteitis deformans of Paget, owing to the fact that it requires totally different remedial measures.

**SYMPTOMS.**—Osteitis fibrosa cystica is usually located in the femur, humerus and tibia, and is commonly the result of traumatism. It is characterized by the presence of a cyst, containing a gelatinous or thin reddish yellow fluid. The bone cortex, having lost its vitality, is easily crushed, the overlying periosteum being readily detachable. This is the most common non-malignant lesion of osseous tissue.

The lesion is usually observed in children. The clinical history is of long duration, pain being but slight, if present, unless there be a fracture, which is relatively common. Some swelling and deformity may be present.

**DIAGNOSIS.**—Osteitis fibrosa cystica may be confused with osteosarcoma, but the X-ray makes it possible to recognize the difference between them. In sarcoma there is usually no bowing of the shaft, which is common in osteitis fibrosa. While the cysts of the latter are clearly sepa-

rated by trabeculae of hard bone with clearly defined edges, the sarcomatous picture is diffuse. The prolonged history of osteitis fibrosa cystica also affords help in identifying the nature of the disease.

**TREATMENT.**—This consists of **rest in bed** for many months, the osseous lesions tending to heal spontaneously. A small cystic area may be opened and the **cyst emptied with the curette**. Sisk (Surg., Gyn. and Obst., Oct., 1925) advises that the cortical canopy be crushed in and that **bone chips** be introduced into the cavity, thus hastening the healing process. The chips may be readily obtained from the surrounding normal bone. If proper precautions are taken to prevent infection the average lesion will, as observed by Sisk, heal by first intention.

### OSTEOMYELITIS.

**DEFINITION.**—As its name implies, osteomyelitis means an inflammation, which may be acute or chronic, localized or diffuse, of osseous tissue and marrow.

**SYMPTOMS.**—These vary according to the cause. Thus, an acute osteomyelitis without bone injury may give rise to sudden and severe symptoms, ushered in by a chill and elevated temperature, violent pain in the bone, and acute tenderness. A blow in the affected area, or sitting in a draught, or a cold plunge after being overheated, etc., may be the starting-point of the morbid process.

In infants and young children the epiphyseal cartilage may be involved, and the pain include or be centered about the neighboring joint, causing exudative arthritis and marked swelling.

The writer observed 12 cases of osteomyelitis in infants less than 1

year old. The morbid process, principally of streptococcic or pneumococcic origin, was always located in the epiphyses, extending frequently to the joint, and causing an exudative arthritis. Two died; 9 recovered completely; in 1 infant a grave lesion developed a year later in the hip joint. Many dislocations of the hip joint, considered as congenital, are probably secondary to an untreated osteomyelitis in infancy. V. Moltschanoff (Russk. Klin., i, 330, 1924).

The relative infrequency of osteomyelitis in children is largely a cause of many mistakes in early diagnosis. To avoid errors and delay it is advisable to regard as osteomyelitis all acute febrile cases, especially in children, exhibiting pain and inflammatory changes in the region of the epiphysis. There is a rich blood supply adjacent to the epiphyseal cartilages, most of which does not come from the nutrient artery but from vessels that encircle the growing end of the bone and send branches of considerable size directly to the epiphyseal plate and adjacent medulla. Chatterton (Minn. Med., Feb., 1925).

Osteomyelitis of the upper jaw is more common in infants than is generally believed. The symptoms include swelling of the upper and lower lips, most pronounced at the internal angle. The pus does not perforate into the nose when it comes from the jaw, but instead into the maxillary sinus. The accumulation and retention of pus may persist obstinately for months.

Osteomyelitis of the upper jaw in infants is more common than is assumed from the cases on record, with 50 per cent. mortality. The writer has himself encountered 4 cases within 18 months and knows of 9 other cases in the Netherlands since 1919. It may appear as early as the 2d to the 10th week. There may or may not be swelling of the cheek, eczema of the lower lid, exophthalmos and invasion

of the ethmoidal or sphenoidal sinus. If it is left untreated, there may be metastases in the lung, heart, meninges or long bones. G. H. Nord (Ned. Tijds. v. Gen., Mar. 29, 1924).

While a mild case may be attended by very slight symptoms and proceed to recovery, the suppurative form tends to cause prominence over the affected area or a fungous abscess into which the probe readily sinks deeply. Periostitis, which is invariably present, may, however, mask the true nature of the case. After the femur and tibia, the vertebræ are the most frequent seats of this affection; an abscess forms, which tends to break down the vertebral column, or bring about meningitis and myelitis by penetration, and thus cause paraplegia. Curvature of the spine is seldom observed, however. Severe cases may end fatally as a result of pyemia or septicæmia. Early in a given case the X-rays afford no diagnostic information.

At the beginning of an osteomyelitis the infection is circumscribed. The painful limb should be gone over carefully. When one reaches a point that is especially painful, that point contains the primary infection. An X-ray picture of it will mislead until the condition has advanced to such an extent that it is far beyond the point at which the patient should be well. It cannot show osteomyelitis until there has been destruction of bone, and at first there is a simple inflammation. Ochsner (Journal-Lancet, July, 1923).

Osteomyelitis, especially the *acute* form, is often confused with rheumatism or arthritis because of a swollen joint, while, if the arthritic phenomena are missing, the febrile course may suggest typhoid fever. Osteomyelitis involving the hip-joint may also suggest a tuberculous process, *i.e.*, hip-joint disease.

Within three days of the initial symptoms pus accumulates in the medullary cavity and causes considerable damage in the surrounding osseous tissue. The overlying surface then becomes discolored, swells, appears glossy, and shows distended veins and edema. The underlying abscess may then reach the surface and rupture spontaneously, infiltrating also neighboring structures, the periosteal and osseous tissues, and the epiphyses. The disease, as a rule, begins, in fact, near the epiphyseal line, the seat of growing bone. Erysipelas, due to involvement of the lymphatic tissues, may occur and aggravate greatly the prognosis.

Acute osteomyelitis varies much in severity, from a mild local infection of a single bone to an overwhelming septicemia with infection of many bones and death in a few days, but the milder forms are more common than the severe.

In the *chronic* form, the local symptoms, pain, tenderness and swelling, are present, but the process is more localized and there are, as a rule, no constitutional symptoms of note, though the condition may have been preceded, perhaps, by fever. On the whole, the chronic form, after some traumatism, develops insidiously and tends to endure as a chronic localized disorder.

Case of acute osteomyelitis of the patella in a boy aged 13, characterized by sudden onset and rapid course. The joint was full of staphylococcal pus 8 days after the first symptom. The writer has collected 50 cases of the same type. There was a history of trauma in 24, but usually the infectious process developed spontaneously. The osteomyelitis was acute in all but 5 cases. The operations were completely successful in 24; in 10 there was more or less stiffness, and in 3,

complete ankylosis. Regeneration of the patella may be anticipated when the cartilage protecting the cavity of the joint and the fibrous periosteal envelope have been saved. Rocher (Paris méd., July 21, 1923).

### ETIOLOGY AND PATHOLOGY.

—Osteomyelitis may be caused in various ways. The localized form is usually due to some traumatism, a wrench, contusion or fracture. It may not be due to bacterial infection. The simple diffuse form may also be caused by rickets or osteitis deformans, with bending if located in a long bone.

In cases due to bacterial infection, the pathogenic organism or organisms may gain entrance through some solution of continuity in the tissues due to injury, a penetrating wound, fracture, amputation, bruises, excoriations, suppurating cutaneous areas, etc., by way of the lymphatic system or the blood. Pyogenic foci in the tonsils, sinuses, lungs, pleura, genital or urinary organs, and various febrile diseases, including, besides those previously mentioned, smallpox, diphtheria, measles, and influenza, are all capable of causing osteomyelitis.

Many kinds of organisms may thus provoke the disease. While staphylococci, both aureus and albus, predominate, a mixed infection with streptococci is especially malignant. Mixed infection may also occur, however, with typhoid bacilli, pneumococci, tubercle bacilli, gonococci, and other organisms. The germs locate where traumatisms or interference with the blood or lymph vessels cause either changes in the structure of the tissues, hemorrhages, or extravasations. In all such locations cocci multiply, creating a focus, foci, or widespread infection.

A more or less widespread pyogenic process in the tissues, including sloughing of the soft portions with gangrene, detachment of the periosteum from the bone, the formation of sequestra, etc., may provoke more or less marked constitutional symptoms, due in severe cases to septic infection. Central necrosis and death of the entire shaft of the bone may occur, the morbid process entailing a fatal ending in a large proportion of cases, *viz.*, about 33 per cent. where early surgical intervention has not prevented it.

**TREATMENT.**—In *acute osteomyelitis* prompt surgical treatment is forcefully recommended by all leading surgeons. The acute form, without an open wound, is often so rapidly fatal that operation is advised as soon as possible after the initial chill, which is followed within 48 to 72 hours by the formation of pus in the medullary cavity. By means of a trephine, chisel or burr, the **medullary cavity** should be **opened and drained** either to prevent pus formation or, if pus is already present, to evacuate it. This will usually suffice to forestall all danger.

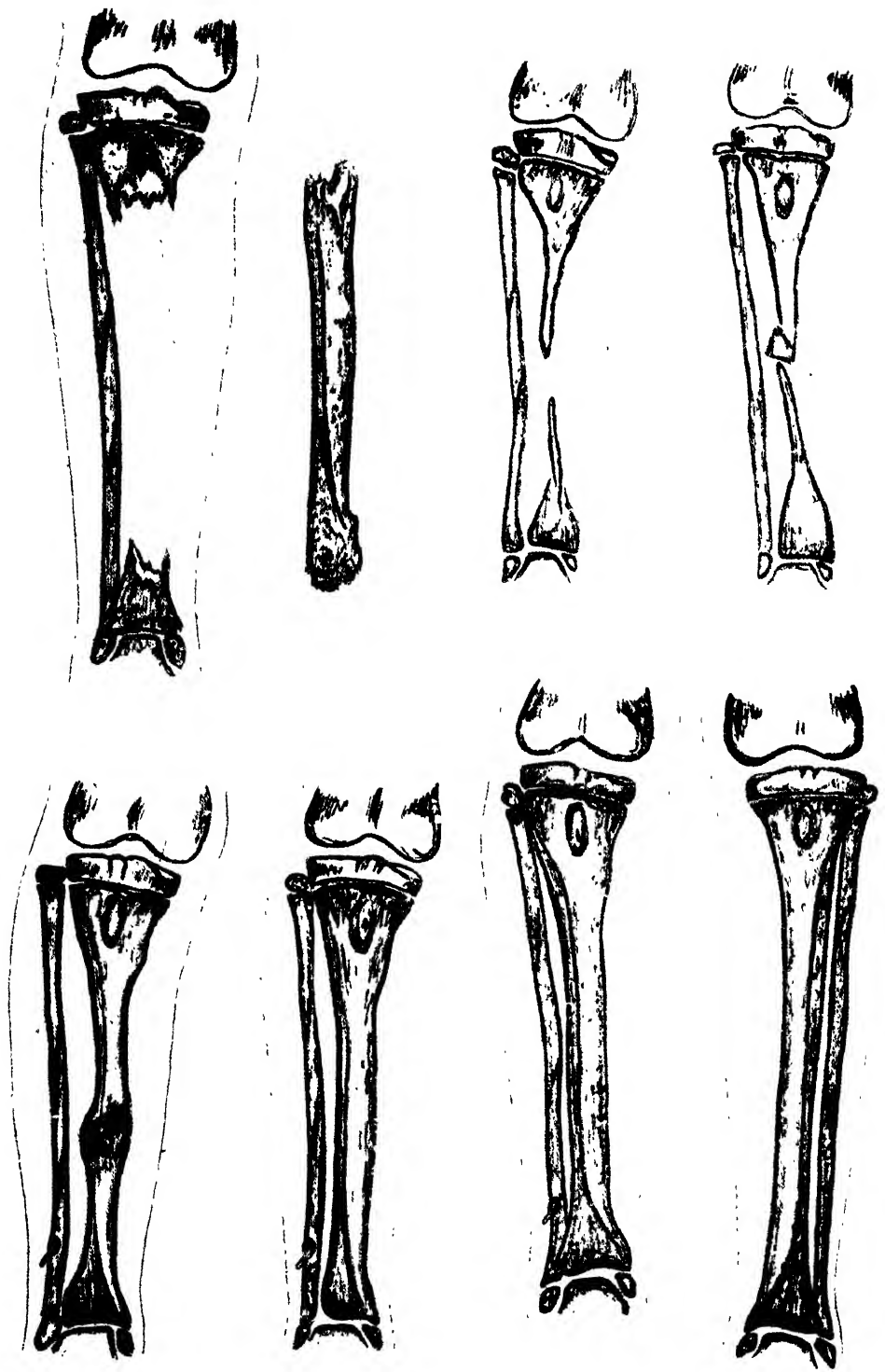
When acute osteomyelitis is due to an open injury or wound, **removal of bone fragments** under strict **asepsis** and with the use of a **tourniquet** to prevent hemorrhage; **irrigation** of the cavity with **hot saline** or **mercury bichloride solution**; scraping it with **gauze bits**, then painting it with **pure phenol**, should be resorted to. The wound should thereafter be packed lightly with **iodoform gauze**, dressed with **hot antiseptic fomentations**, and finally, **absolute rest** to the part insured by the application of **splints and bandages**.

A new method of treating osteomyelitis and bone necrosis which is very simple consists of making a number of small holes in the bone, perforating somewhat like a grater, over the entire exposed part, from 3 to 4 mm. apart. Their depth depends on the thickness of the necrosed bone or, in the case of osteomyelitis, on the thickness of the external part of the bone as far as the medulla. In cases of necrosis, trephining of the bone should be done without an anesthetic, because if the bone is really dead there is no sensation. In the cranium, of course, only the external table is perforated. The perforations facilitate the penetration of granulations into the bone so that in a short time they cover all the exposed part and skin may be grafted from the vicinity. The writer used this method successfully in 7 cases, comprising 4 of necrosis of the tibia, 1 of cranial denudation, and 2 of acute osteomyelitis of the femur. The necrosed bone in all cases was resorbed and its place taken by bone cells of new formation. A. L. Soresi (Arch. di ortop., xxxiv, 338, 1919).

When dead bone has formed the **medullary cavity** should be **opened and curetted**, the sequestrum being removed. The wound is then drained. When a joint is involved, that of the hip, for example, it is important to save, if possible, the connecting bone, such as the neck of the femur in this instance. Hence the importance of **early intervention**, with **rest and tonics** to support the general state of the patient. The **hypophosphites** are helpful adjuncts in this connection, assisting as they do in bone repair. Neglected cases may lead to the necessity of **amputation**.

The writer advocates the use of an **autogenous vaccine** in staphylococcal osteomyelitis. An initial dose of 200 million is given; on the 3d day a dose of 400 million is used, and this is repeated on the 5th day; thereafter the





Regeneration of the tibia in a boy. (*J. A. Hutchinson.*)  
Montreal Medical Journal.





restoration of normal function than the less radical procedures. Bauman and Campbell (Surg., Gyn. and Obst., Jan., 1926).

In *acute hematogenous osteomyelitis*, according to C. L. Starr, the bacteria lodge in the finer capillaries of the juxta-epiphyseal region of a long bone. Pus is formed and, contrary to general belief, the infection works its way more rapidly to the periosteum than into the medullary canal. X-ray findings are always negative at first and show no changes until there has been gross destruction of cancellous bone, when they are no longer of diagnostic value. In the treatment an incision should be made through the periosteum to the bone over the area of greatest tenderness, keeping the incision on the diaphyseal side of the epiphysis. If pus is met with, this incision is sufficient; if not, the periosteum should be stripped for a short distance to make sure that the incision has not been made at the wrong point, and 3 small drill holes,  $\frac{1}{4}$  inch apart, made in the bone obliquely downward to the epiphyseal line. In 6 patients thus treated the wounds healed in 3 or 4 weeks without sequestration.

### BONE TUBERCULOSIS.

**DEFINITION.**—A chronic tuberculous inflammation of the osseous structures, limited to the cancellous tissue in most instances.

**SYMPTOMS.**—Early recognition of bone tuberculosis is usually very difficult, so insidious is its onset. The slight general manifestations, especially the unimportant temperature changes; the local tenderness and enlargement, which in the case of fingers is sometimes considerable before actual suffering is induced, coupled with the

general appearance of the patient and a family history of tuberculosis, may facilitate recognition of the true nature of the morbid process.

Pain in the affected region, stiffness of the overlying muscles and of the nearest joint, localized tenderness to pressure, and slight increase of local temperature constitute the first series of symptoms observed. The pain is deep-seated, but not sharp; the tissues may feel boggy and are sometimes slightly tumefied, owing to interference with the circulation, as indicated by the enlargement of superficial veins occasionally observed.

As long as the inflammatory process is in its incipency, the general health does not suffer. As soon as the bone-tissues begin to disintegrate, however, and pus and tuberculous deposits are formed, and caseation occurs, the local manifestations become decidedly more marked and general symptoms appear and slowly increase: The pain is much greater; pus-channels and fistulæ are formed. When the purulent products are evacuated through the latter, however, the general health of the patient may become improved.

The fact that the disease may be arrested by removing the foci of infection indicates the pathogenic influence of the local process upon the general organism and the likelihood of encountering symptoms due to them. The vertebræ, the upper end of the femur, the bones of the hands and feet, and the elbows are the regions most frequently involved. Under **SPINE, DISEASES OF; HIP-JOINT DISEASE, and JOINTS, DISEASES OF**, this important subject is fully treated. The *spina ventosa* of the fingers is a tuberculous disorder.

A study of the records of 22,233 cases of tuberculous bone and joint disease by Terry and Allison showed that in 39.1 per cent. the localization was in the spine; in 31.4 per cent. in the hip, while the remaining 29.5 per cent. was divided among the knee, ankle, elbow, wrist, and shoulder in the order named, the knee being involved in 1827 cases and the ankle in 919 cases.

Modern laboratory methods (see TUBERCULOSIS in Volume VIII), by increasing its safety, have caused the Koch tuberculin test to be used with greater frequency in recent years. The methods of Pirquet and Moro are only fairly reliable and satisfactory, though not dangerous.

Local reactions to inoculations of both human and bovine tuberculin were invariably present in all patients from whose pus tubercle bacilli had been isolated. Yet the degree of reaction varied within wide limits: Weakly and cachectic patients usually reacted feebly, irrespective of differences in the severity of their local lesions; strong and vigorous patients exhibited wide differences in the degree of their reactions, likewise irrespective of differences in the extent or the severity of their local lesions. H. J. Gauvain (Lancet, Oct. 6, 1917).

Applying the *tuberculin test* in 200 cases of bone and joint disease, the writer obtained a positive focal response in only about 66 per cent. of the cases of surgical tuberculosis. A negative response to various tuberculin tests, in his opinion, positively excludes tuberculosis. Mau (Deut. zeit. f. chir., Mar., 1921).

Results of *tuberculin tests* in 200 cases of presumably tuberculous bone and joint diseases in children. Positive reactions were obtained in all but 7 cases, with the following percentages: Skin test, 93.03 per cent.; intradermal test, 75.25; ophthalmic, 33.15, and the Moro percutaneous inunction test, 56.72. Of the 7 negative cases, 5 were shown to be non-tuberculous hip conditions by the subsequent course, while in 2 the negative results were ascribed

to advanced cachexia. R. Egaña (Semana méd., June 28, 1923).

The presence of tubercle bacilli in blood treated with an alkaline solution of sodium hypochlorite has also been recommended in recent years, on sound premises. In addition, the calcium level is markedly raised, particularly where considerable tissue has been broken down.

In spite of X-ray examination, guinea-pig inoculations and histologic study, the writer frequently found the diagnosis merely presumptive. Study of the sedimentation of the red cells is of greater service in ascertaining the degree of activity and intensity of the tuberculous process than for differential purposes. S. Johansson (Svenska Läk. Handl., June 30, 1924).

In the blood of children suffering from tuberculosis of bones, the writer found slight changes of the potassium and magnesium content. The sodium was slightly and the calcium markedly increased. With grave destruction of bone tissue, the calcium level was almost twice as high as normal. A. Muggia (Riv. di clin. ped., Feb. 20, 1926).

**ETIOLOGY.**—Though injury often plays a conspicuous part in the commencement of bone tuberculosis, it is only a contributory factor, providing a suitable nidus or soil in which the tubercle bacillus develops and produces its destructive effects.

The affection does not appear to start from severe injuries, but from slight ones that cause but little disability at the time of their reception.

While in some cases of bone tuberculosis the lungs are primarily affected, in by far the majority the infection is probably derived primarily through other portions of the respiratory or alimentary tract, especially the tonsils, nose, throat, intestines, bronchial glands, etc.

Tuberculous foci may form in any part of the bone, but particularly in the epiphyses or the spongy portion of the shaft near the epiphyseal cartilage. At first limited to the size of a pea, perhaps, the focus gradually enlarges; other foci are then formed, which coalesce. Several general foci of infection may thus be formed, all containing the bacillus of tuberculosis. The detritus may become transformed into a cheesy or liquid mass; if this does not occur, a sequestrum is formed, which sooner or later becomes free in the cavity, surrounded by caseous pus. The reparative process consists in inclosure of the cavity in sclerotic bone-tissue, and an ivory-like envelope may thus be formed around the tuberculous cavity. In other cases a limiting pyogenic membrane is generated. Fistulous tracts are developed from these cavities, the pus breaking its way outwardly.

The general etiology of tuberculosis *per se* is treated in the article on TUBERCULOSIS in Volume VIII.

**PATHOLOGY.**—While hyperemic thickening of the periosteum and its underlying tissues is an early sign of bone tuberculosis, the tuberculous process originates within the bone itself. It may be primary, a single focus being found in the cancellous tissue, as is the case in the form known as *spina ventosa*, but in the majority of instances the tubercle bacilli reach the osseous tissue through the soft tissues, the blood or lymph being the chief intermediaries.

While the bone marrow resists infection when normal, it becomes more susceptible to it when diseased or impaired by traumatisms, often through lesions of its vascular supply. The infected area becomes soft and

spreads, including neighboring areas, and may thus be transformed into a confluent mass of broken down tissues. This is due, from my viewpoint, not to the bacteria, as is now believed, but to digestive, *i.e.*, defensive enzymes brought there by leucocytes which subject all substances, including the bacteria, to hydrolytic destruction. Hence the presence in the magma of necrotic tubercle pus cells rich in trypsin, etc. The elimination of this detritus occurs through suppurative abscesses or absorption if it be small in quantity.

The formation of new bone cannot occur without that of sequestra attached to one or more points to provoke constructive irritation, osteoclasts intervening to soften the osseous tissue by taking up its calcium, while osteoblasts rebuild the bone.

**TREATMENT.**—The modern treatment of tuberculosis of the bones is based upon **open-air life**, with **sunlight** as direct curative agent, and **ample food and rest of the affected part** as dominant factors.

As regards sunlight or **heliotherapy**, my own labors have shown that the great benefit it procures is due to the heat-energy it develops in the tissues. As the wave-length of the solar rays increases from violet toward red, their photochemical activity is gradually lost, but they simultaneously develop both *penetrating and heating power*. They enhance in the diseased tissues, therefore, the defensive process by increasing the bactericidal and anti-toxic activity of the defensive enzymes which promote the destruction of the tubercle bacilli. This process, which I described briefly in the Medical Journal and Record of September 15, 1926, belongs essentially to the en-

doctrinological and physicochemical fields.

Some physical laws must be borne in mind in this connection. The ultra-violet rays do not penetrate deeply into the skin, but they activate pigmentation. This serves, as in the negro, to protect the deeper tissues from the destructive photochemical effects of sunlight. Graduated exposure of the patient's body to sunlight is necessary, therefore, to cultivate pigmentation, since when the skin is brown it is better able to stand prolonged and more effective exposure to the sun. Simultaneous exposure to the open air is a necessity, however, if the best results are to be obtained for, as the skin is being heated, the air covering it should be in motion in order to insure dissipation from the surface of the surplus of the unabsorbed heat energy. Thus employed, as in well organized establishments, heliotherapy becomes a pleasure to the patient. Especially is this the case when it is conducted at the seashore, though excellent results are also obtained in the mountains.

A formal **fresh air and sunlight treatment**, as elaborated at Berck-sur-Mer near Boulogne, France; Leysin in Switzerland; Sea Breeze at Coney Island, Southampton, N. Y., and elsewhere, has been the most important advance in bone and joint tuberculosis in a generation, as urged by H. Ling Taylor. Sunlight causes peripheral or local hyperemia and is bactericidal. Exposure of the skin to air is in itself beneficial. Rollier begins by gradually exposing the affected area for 5 minutes and increasing the area and the time until a complete exposure is obtained for several hours. Children under the writer's care have been exposed entirely nude for 6 hours a day in the summer with the greatest benefit. Burning of the skin by too energetic treatment may be avoided by the free employment of talcum powder for the first week.

Extensive experience has shown that combined **heliotherapy** and **seashore** environment represents the most energetic treatment at our disposal for tuberculosis of bones and glands. The writer does not place much reliance on drugs. Autoinoculation with fluid from the diseased joint has been abandoned. Serotherapy has given inconstant results and, as is the case with tuberculin, is still on trial. This applies also to high frequency currents. Sorrel (*Presse méd.*, Feb. 5, 1921).

One must be somewhat careful in the application of sunlight and not rush matters too much in the beginning. The point is to achieve a tan and not a burn. Blondes do not tan as readily as brunettes, and in blondes one must be more careful in the gradual application of sunlight. The patient's eyes and head must be protected; no exposure should take place after meals.

The application of sunlight to these tuberculous patients immediately increases the appetite and a gain in weight is noted. Within a few weeks freedom from pain and a general condition of well-being and cheerfulness has established itself. The patient becomes accustomed to his new environment and sleeps and feels well. *Fistulæ* usually close, sometimes with surprising rapidity. Deformities often disappear, especially in the young. By means of heliotherapy, tuberculous joints may frequently "heal out" with painless motion. Geist (*Minn. Med.*, Apr., 1923).

"**Helio-marine therapy**" acts solely by stimulating all the natural reacting potencies. Among the author's 85 cases, 94 per cent. of the 33 patients with closed lesions were completely cured, and 63.24 per cent. of the fistulous cases. In only 1.48 per cent. of this group did the lesion continue a progressive course. The patients were in the sanatorium for an average of 1 year in the cured cases. Vayola-Coco (*Chir. degli org. di movimento*, Oct., 1925).

Ample and **nourishing food**, of which eggs, the yolks of which are

rich in the phospholipoid lecithin, are to form part, is an important adjunct, since the curative process requires various factors which the foods alone afford. The meals should be made agreeable to the patient.

The use of **tuberculin** is advocated by some clinicians but deemed useless by others. The whole question, therefore, is still unsettled. Its proper place is probably as an adjunct to the measures described, to hasten the curative process.

Under modern **tuberculin** treatment the author's recoveries in bone and joint tuberculosis have averaged 68 per cent., as against 34 per cent. when treated without tuberculin. In addition, the period of treatment of recovered cases averaged only 11½ months, as against 5¼ years without tuberculin. Tuberculin checks the local process, the individual also regaining and maintaining strength not attained by treatment alone on general hygienic and orthopedic lines. Twinch (*Amer. Jour. Orthop. Surg.*, Sept., 1918).

Experience has shown that **tuberculin** does not cure tuberculosis of the bones and joints, and in the majority of cases causes no noticeable beneficial influence upon the lesions, though in a small proportion of cases there is improvement. In some, on the other hand, there may be a distinct accentuation of the disease. Relapse may occur after apparent improvement. Kleinberg (*Jour. of Orthop. Surg.*, Dec., 1919).

**Rest, heliotherapy, tuberculin** and **general hygiene** are the procedures of greatest importance in bone and joint tuberculosis in children. In using **tuberculin**, the writer begins with ½<sub>20,000</sub> mgm. of B. F. (bouillon filtrate) subcutaneously and increases up to ¼<sub>100</sub> mgm. in about 3 months. **Heliotherapy** in addition shortens the course of the disease and improves the general condition. W. A. Clark (*Jour. of Bone and Joint Surg.*, Oct., 1923).

The use of **codliver oil** is as important in this connection as in any other manifestation of tuberculosis. It increases both the serum and bone phosphorus ratio and promotes the deposition of calcium in the bones. While **sunlight** supplies heat energy, **fresh air** affords an abundance of oxygen, a scientific triad as sound as it is effective.

An important feature of the treatment is **rest of the diseased part**, procured by means of a **brace** or **fixation splint**, and also of the patient himself if there is any degree of fever, with ample **fresh air** circulating about him, though avoiding drafts. A tent, porch, or even an open window with one of Knopf's inclosures will serve the purpose admirably. The patient, provided there be no fever, should then be given **massage** if abed, the best being **gentle pétrissage** of the normal tissues, or may be allowed discreet and non-tiring **exercise** if he can readily perambulate.

Various local measures have been tried and eventually abandoned. A few, however, have held their own. Notable among these are injections of **iodine** in 10 per cent. solution. From my viewpoint this is accounted for by the fact that iodine is not only antiseptic but an activator of the defensive process, emulating in this respect the thyroid hormone itself.

The method of Durante, which has been used on a large scale with satisfactory results, consists of injections of **iodine** and **potassium iodide solutions** under the skin, into the muscles, and into the cavities and sinuses. The action of **iodoform emulsion**, which has so long been used for this purpose, is due to the liberation of iodine. But this takes place very slowly in the tissues at the normal temperature. The iodine-potassium-iodide solution, however, is much more prompt and efficient:—

R *Iodine* ..... 4½ grs. (0.3 Gm.).  
*Potassium iodide* ... 45 grs. (3 Gm.).  
*Glycerin*,  
*Distilled water*, of  
 each ..... 750 mins. (47 c.c.).

M.

Delbet (Bull. de l'Acad. de méd., Dec. 1, 1925) recommends the Finikoff method, *vis.*, the use of a 10 per cent. mixture of tincture of **iodine in oil** for intramuscular injections, given at 5 or 7 days' intervals, at points remote from the lesion. The first injections each consist of 10 c.c. (2½ drams); the next of 20 c.c. (5 drams). The treatment lasts 6 or 8 months. **Calcium chloride** is administered simultaneously by the mouth. In tuberculous abscesses or multiple sinuses, and in tuberculous hydrarthrosis or arthritis, a clinical cure resulted. Seemingly inevitable amputations were averted. Finikoff aims to enhance the lipolytic power of the mononuclears and the proteolytic power of the polymorphonuclears.

The ultra-violet rays, the **X-rays** and the **infra-red rays**, the latter to allay pain, have also had advocates. The best results were obtained, however, when they were used in conjunction with heliotherapy, fresh air and copious food.

In bone and joint tuberculosis, the writer used very effectively the **ultra-violet rays** in 200 cases, beginning with a 1-minute exposure to the mercury quartz lamp at a distance of 50 to 70 centimeters, and later increasing the time by 1 minute at each exposure and decreasing the distance progressively to 20 or 30 cm. Two or three treatments a week are given. When erythema appears, the dose is cut down ½, then later increased again up to the skin dose. The **X-ray** is also sometimes used for deep, localized effects and the **infra-red rays** to allay pain. Saidman (Presse méd., July 2, 1924).

**Operative measures** may prove of great value. If the local condition is acute, the active symptoms may often be made to subside at once by drilling a half-dozen holes 3 mm. in diameter into the part for a local depleting

effect, and then encasing the limb in **plaster of Paris**, thus keeping it at absolute rest. The affected area of bone may also be removed by the gouge and the use of the curette. This must be done thoroughly, however, every vestige of diseased bone or its contents being carefully removed. The same radical measures should be used in adjoining cavities or surfaces. The cavity should then be filled with **iodoform** or **bismuth paste**. After operation scrupulous care must be taken to insure absolute quiet of the part with **fixation splints**, usually of plaster of Paris.

Where there is delay in healing, the ulcerated surface should be touched up with the solid stick of **silver nitrate** every 2 or 3 days.

Very few cases nowadays cannot be satisfactorily treated without **amputation**. Of late **periarterial sympathectomy** has been proposed as a possible means to avoid amputation.

The writer would reserve **periarterial sympathectomy** in tuberculosis of bones and joints for the grave cases with fistulas, as a last conservative resource before amputation. It is superfluous and sometimes harmful in closed tuberculosis. Zahradnický (Casopis lek. cesk., Oct. 3, 1925).

C. E. DE M. SAJOUS,  
 Philadelphia.

**BORIC ACID.**—Boric or boracic acid [ $\text{H}_3\text{BO}_3$ ] appears in the form of white, translucent or lustrous scales, or a powder. It has a faintly bitter taste and a feeble acid reaction with litmus. It is soluble in 18 to 26 parts of water at 25° C., in 4 parts of boiling water, in 15 parts of cold alcohol, and in 4½ parts of glycerin; it also dissolves in chloroform and in oils. Addition of hydrochloric acid decreases the solubility of boric acid in water.

Heated to 100° C., boric acid loses water, passing into metaboric acid [ $\text{HBO}_2$ ], which becomes slowly volatilized. On boiling a solution of boric acid, it escapes with the steam. An alcoholic solution of the acid burns with a green flame—a fact which affords a ready means for detecting it.

#### PREPARATIONS AND DOSE.—

Besides the acid itself, *acidum boricum*, the dose of which is from 5 to 15 grains (0.33 to 1 Gm.), the following are official preparations:—

The *glyceritum boroglycerini* (the glycerite of boroglycerin), composed of boric acid 310 parts, glycerin 690 parts. Employed externally.

The *unguentum acidi borici* (ointment of boric acid), an ointment of petrolatum and yellow wax, containing 10 per cent. of boric acid.

The *sodii boras* (sodium borate or borax), a colorless or white crystalline powder, having a sweetish taste, soluble in 16 parts of water, 1 part of glycerin, but not at all in alcohol. Dose, 5 to 20 grains (0.33 to 1.3 Gm.).

Recognized in the National Formulary is:—

The *liquor antisepticus*, N. F. (antiseptic solution), containing 2.5 per cent. of boric acid, with small amounts of antiseptics and aromatics, such as thymol, eucalyptol, methyl salicylate, menthol, and oil of thyme.

**INCOMPATIBLES.**—Boric acid is incompatible with carbonates and bicarbonates, and the alkaline earthy and metallic bases. Sodium borate is incompatible with the acids and metallic salts, and precipitates cocaine and morphine in solution.

#### PHYSIOLOGICAL ACTION.—

Boric acid and all its salts are deemed more or less antiseptic, and the for-

mer has attained special repute because of its inexpensiveness, general harmlessness, and supposed unirritating character, virtues which in reality apply only to weak solutions. But purity is always to be carefully considered, both as regards external and internal use. It is not so commonly employed as an internal medicament, perhaps, as the sodium salt, because of its somewhat pungent and acid taste, and partly because it is deemed less convenient to prescribe in aqueous mixtures. In large doses, however, both it and the salts depress the spinal centers, and may produce progressive loss of voluntary and reflex activity without affecting nerve or muscle. Schiff found that boric acid, when locally applied to nerves, caused the part to lose the power of originating, but not of transmitting, impulses; so that, if the galvanic current be applied to the part of the nerve which has been exposed to the drug, no muscular contractions result; but, if the poles be placed above this part, the distal muscles respond at once. Boric acid and, to a less degree, sodium borate retard the diastasic action of the saliva upon starches, while increasing, according to some observers, that of the pancreatic products. This probably applies, however, only to small doses, for it tends, in moderate doses, to delay absorption of both proteins and fats.

In large doses often repeated, boric acid is likely to induce nausea and vomiting, and, if persisted in (or even in large, single doses), to check gastric digestion and give rise to a concatenation of symptoms indicating gastroenteritis by a direct action, as shown below. Both boric acid and sodium borate also tend, in large



doses, to promote contraction of the uterine muscle, and may thus act as an echolic.

Diuresis with increased desire to urinate has been found to follow doses of from 30 to 120 grains (2 to 8 Gm.); the acid is eliminated through the kidneys, causing albuminuria in persons predisposed to it, and also escapes with the perspiration, saliva, and feces. It enhances the elimination of urea, as well as the flow of urine.

**POISONING BY BORIC ACID AND SODIUM BORATE.**—The symptoms of poisoning are, briefly, a sensation of severe uneasiness in the stomach and intestines, with dryness of the throat, difficulty in swallowing, nausea, vomiting, diarrhea; headache, with dimness of vision, and somnolence, lassitude progressing to intense weakness, leading to collapse and even death.

Case of poisoning in an 8 months' old baby, due to milk given which contained boric acid, 5 grains (0.3 Gm.) to the pint (500 c.c.). The child had been taking from 7.5 to 10 grains (0.5 to 0.65 Gm.) of the preservative daily. A new supply of fresh cow's milk caused the symptoms to cease and within a couple of days the child began to get well, though it was some months before it was normal again. Forsyth (*Lancet*, Oct. 25, 1919).

Though some authors insist that very large doses are necessary to produce dangerous symptoms, this is not supported by general evidence, for it has been known that relatively small doses suffice to induce the above phenomena, and also nephritis. This is especially true of the sodium salt, which is a dangerous remedy as regards most renal disorders, and seems to possess the power of provoking de-

generation where a morbid process has already been set up in the kidneys. Cases have also been reported in which the local application of powdered boric acid produced general toxic symptoms: in one case the skin had a dried, "charred" appearance, and in the other there was collapse; in 2 there was very marked coolness of the vagina, to which it had been applied on a tampon. A bluish-gray line on the gums, as if from lead poisoning, has been observed in a case of epilepsy to which sodium borate had been given. Cases have also been reported as poisoned through the daily application of 30 grains (2 Gm.) of the acid. In one case there were restlessness and a feeling of burning under the whole skin, intense thirst, a temperature of 38.8° C. (101.8° F.), and the body covered with red patches; in another case an eczematous eruption, anorexia, and insomnia appeared. In both cases the untoward symptoms subsided immediately on withdrawing the acid applications. What is said of the acid applies, in a general way, to its salts.

Boric acid and borax do not belong to the class of substances that are inactive and without danger. H. Rost (*Deut. med. Woch.*, Feb. 12, 1903).

Case of fatal boric acid poisoning. The inguinal glands had been excised and the cavity packed with about 6 ounces of boric acid powder. Soon after the operation the man developed the typical signs of boric acid poisoning: profuse vomiting; a papular rash over the face, neck, and chest, and a weak, irregular pulse. The onset was rapid and the fatal issue came on within four days. There was also delirium and slight rise of temperature. C. I. Best (*Jour. Amer. Med. Assoc.*, Sept. 17, 1904).

Case of a 2-year-old child suffering from a burn measuring 12 to 13 cm.

To this, fresh boric acid ointment was applied. Soon there appeared a scarlatiniform rash, petechiæ, and evident head symptoms. Three days later the child died. The possibility of children having an idiosyncrasy for this drug warns against the danger that may ensue upon its use in burns or in other cases where a raw surface favors absorption of the drug by the patient. Dopfer (*Münch. med. Woch.*; *Der Kinderarzt*, Feb. 2, 1906).

Case of boric acid poisoning from the use of rectal irrigations of boric acid solution in dysentery. There appeared a rash resembling a bromide rash, delirium, and feeble pulse, suddenly and without warning. The eruption persisted after all drugs had been stopped. J. H. Sanders (*Brit. Med. Jour.*, March 16, 1912).

The writer formerly used boracic acid solutions for lavage of the bowels in cases of colitis, but after having seen symptoms arise in at least 3 patients, decided it might not be such a harmless method as one would be inclined to believe. Harley (*Brit. Med. Jour.*, Apr. 13, 1913).

Case of a baby 7 weeks and 6 days old who was given about 3 ounces (90 c.c.) of a saturated solution of boric acid instead of boiled water. It vomited while being nursed, so that this was discontinued, and 3 more ounces of the boric acid solution were given. Copious movements followed, which soon became nothing but clear, jelly-like mucus, and vomiting continued for about 36 hours, gradually decreasing in severity. Two days after the first ingestion there appeared a slight miliary eruption on the neck, chest and back. The disease ran its course rapidly and the peeling was completed in about 10 days. The baby rapidly recovered. P. Wilson (*Wash. Med. Annals*, Nov., 1915).

**TOXIC EFFECTS OF BORIC ACID AS A FOOD PRESERVATIVE.**—Boric acid plays no part in the vital process; but it destroys life even in weak solutions. Hoffmann

(cited by Franz, *Deut. med. Woch.*, Bd. xxviii, p. 832, 1902) has shown that fish die within two days in a solution of boric acid as weak as  $\frac{1}{4}$  (0.25) of 1 per cent. Not only were severe intestinal disorders produced, but the outer skin was itself inflamed. When the relative sensitiveness of the mucous membrane of the alimentary canal of those infants and individuals who depend solely upon cows' milk for sustenance is taken into account, the judgments of English courts against dealers who had sold milk containing as small proportions of boric acid as  $\frac{1}{30}$  and even  $\frac{1}{37}$  of 1 per cent. (*Brit. Food Jour.*, vol. x, p. 212, 1908; vol. xi, pp. 10 and 15, 1909) are fully warranted. That such limited adulteration renders milk or cream poisonous is beyond doubt. Fourteen grains (*N. Y. Med. Jour.*, vol. lxxxiii, No. 14, April 7, 1906) in divided doses daily have been found to cause severe gastrointestinal disorders in adults at the end of three days. Now, an average infant 6 months old, fed artificially on cows' milk, consumes 36 ounces a day. With a proportion of  $\frac{1}{30}$  of 1 per cent. of boric acid, a pint of such milk would contain  $2\frac{1}{2}$  grains (0.16 Gm.). As 36 ounces represent 2 pints and 4 ounces, we have an aggregate of 5.625 grains in the infant's daily food, eight times more than necessary to provoke the toxic phenomena in adults referred to above, since an infant 6 months old requires but one-twentieth of an adult dose (Griffith, *Lectures at the University of Pennsylvania*) to show corresponding effects, i.e.,  $\frac{1}{10}$  of a grain (0.045 Gm.) in the present connection. An infant brought up on artificial food, especially among the poor and ignorant, is often given,

with the best intentions, practically anything in the farinaceous line, in the form of soup or pap. Such foods are also used extensively, along with milk, for invalids, particularly those suffering from gastric disorders. A prominent authority, Pouchet, of Paris, holds (*Pharmacologie et matière médicale*, p. 805, 1907), with others of equal rank: Halliburton (*Brit. Med. Jour.*, 1900, vol. ii, p. 1), Weitzel (*Arbeiten aus dem Kaiserlichen Gesundheitsamte*, vol. xix, part 1, 1902, p. 126), that even in minute amounts boric acid interferes with digestion by decreasing the strength of the gastric and pancreatic juices, and urged that its use as a preservative be "rigorously proscribed"; he is suggestively sustained by the many cases of infantile diarrhea traced by Tubb-Thomas (*Public Health*, vol. xi, 1898-99, pp. 528-538) to milk containing this preservative, and by the conclusion of Annett (*Lancet*, 1899, vol. ii, pp. 1282-83-85), after a searching inquiry into the subject, that to such preservatives must be mainly ascribed the great infant mortality during the summer months. While the combination of boric acid milk and boric acid crackers will practically insure death for the unfortunate infants whom mercantile methods will have subjected to such a fate, many of those yet safe because pure milk is still within their reach will be doomed, if their auxiliary foods happen to contain boric acid, even in as small a proportion as  $\frac{1}{20}$  of 1 per cent.

Worthy of note also in this connection is Förster's remark (*Hyg. Rundschau*, 19, 169-185) that the work of mixing (a difficult task) is usually entrusted to careless and

ignorant hands, and that variations of from 1 to 4 per cent. were to be found in treated foods. What guarantee is there under such conditions that uneven distribution will not greatly increase the danger?

But it is not only in the infant that foods containing boric acid are harmful. It applies particularly also to the multitude of sufferers from disorders of the stomach, intestines, and kidneys, and to the neurasthenic and debilitated.

To quote the words of Medical Officer Hill, of Birmingham (*Public Health*, vol. xi, 1898-99, pp. 528-538), "A number of experiments have been made on men and animals by Mattern, Förster and Schlenker, and Chittenden, with the result that they all found that smaller or larger doses interfered with digestion and nutrition." Comparative trials on himself with cream showed Allan (*Brit. Food Jour.*, vol. x, pp. 151, 1908) that dyspepsia appeared only during the periods when the cream contained boric acid. Its evil effects in moderate doses have also been recorded by Kenwood (*Brit. Food Jour.*, vol. x, p. 97, 1908), Merkel (*Münch. med. Woch.*, vol. 1, p. 1, pp. 100-101, 1903; *Lancet*, March 14, p. 749, 1903), and others—indigestion, headache, flatulence, abdominal pain, and diarrhea, ceasing only when the use of boric acid was discontinued. We need not wonder at these effects, since, as shown by Hoffmann, of Berlin (*Deut. med. Woch.*, Bd. xxviii, S. 832, 1902), strong, fresh-caught frogs "placed in a weak boric acid solution" in such a manner that this solution touches only the lower part of the body will soon develop great blisters in the immersed portion, the "epithelial

layers of the skin being then dissolved off so that large pieces float on the liquid." Even when the solution was but *one-half of one per cent.* ( $\frac{5}{10}$  per cent.) the inflammatory process developed, with loss of the same skin tissues on the second day.

This accounts for the most disastrous effect of boric acid: the destruction of the lining epithelium of the intestinal canal, so important in the process of absorption of foodstuffs that its loss means death from starvation. Thus, Hoffmann (*loc. cit.*) found that dogs whose food contained 2.5 per cent. of boric acid showed, *post mortem*, marked lesions of the stomach and intestines. There were necrotic areas, and large pieces of mucous membrane had sloughed off. Similar experiments by Puppe in dogs gave like results, and he compares the action of boric acid to that of corrosive sublimate. In experiments by Pouchet, dogs lost one-fifth to one-sixth of their weight. In man 3 grains (0.2 Gm.) of boric acid daily (many adulterated milks contain more than this proportion to the pint) suffice to decrease the weight, as shown by Rost.

Bright's disease, including the various kidney disorders grouped under this head, is, of all conditions, one of the most seriously aggravated by small as well as large quantities of boric acid. Not only are the kidneys practically the sole organs through which it is eliminated, but they excrete it slowly, so that it requires from five to eighteen days to eliminate even a moderate dose. Used continuously as it is in food, boric acid accumulates in the blood, subjecting the kidneys to constant irritation.

**THERAPEUTICS.**—**Boric Acid.**  
—The germicidal value of boric acid is

limited, since it does not destroy pathogenic bacteria. Yet, it presents the advantage, in 4 per cent. solution, of inhibiting their growth. Hence its wide use for this purpose. The scope of boric acid as an antiseptic has been extensive, *i.e.*, in almost every conceivable surgical condition: as a detergent for painful and suppurating **wounds** and **ulcers**; as a basis for injections and ointments of all kinds; in collyria; as an insufflation powder for the ear; to wash out the bladder in **cystitis** and for a similar purpose in **dilated stomach**; as an application to skin maladies. But the toxic effects described under "Poisoning" should always be borne in mind.

Boric acid has been very extensively employed in the treatment of diseases of the eye. Thus, Bourgeois has recommended it for **phlyctenular** and **granular conjunctivitis**; Smith, as a wash for **ophthalmia neonatorum**. It has also been used as an ointment between the eyelids after operating for **cataract**; but the drug should be used with caution, and of a strength of not more than 1 per cent., since Noyes saw a diffuse keratitis develop from a 4 per cent. solution.

In **measles**, too, frequent bathing of the eyes, nose, and ears with a warm, but weak, boric acid solution is to be recommended as beneficial and comforting to the patient.

This drug has also been employed in the treatment of **chancroid**, as a dusting powder; in **nasopharyngeal catarrh**, especially the troublesome form seldom seen except in children and in **otorrhea**; in chronic **constipation**, by applying the dry powder directly to the rectal mucosa. In a watery 5 per cent. solution boric acid has been extensively employed in

pharyngitis and in mild laryngitis; in aphthæ and other forms of stomatitis, and in ointment form to the urethra for gonorrhea, and also to the pustules of variola to prevent pitting.

Rapid recovery is said to have been obtained in eczema, and also in contagious impetigo, by employing it in glycerole of starch, 1 to 30. In the erysipelas of the newborn, boric acid has been lauded above many other agents.

Saturated solution of boric acid as a wet dressing is almost specific in streptococcus and staphylococcus albus or citreus infection of the skin and cellular tissue, as well as in pemphigus. It is less effective in staphylococcus aureus and entirely without value in gonorrhea, specific inguinal adenitis, chancre, chancroid, pyocyanus and saprophytic infections, and even harmful in malignant edema, tuberculosis, and impetigo contagiosa. Rest, elevation, and elimination by the bowels, lungs, skin, and kidneys should be carried out conjointly. Ninety-five per cent. alcohol added to the boric solution to make it 15 to 30 per cent. alcohol is of great value. An area should not be incised unless there is a collection of pus and then the incision should be kept inside the limits of nature's walled off zone or distal to it. E. H. Ochsner (Ills. Med. Jour., xxxi, 139, 1917).

**SODIUM BORATE; SODIUM BIBORATE; BORAX.**—This, the best known, and most generally employed internally, of all the borate salts, has long been alternately lauded and condemned by the medical profession, though it has always retained a *status* in domestic pharmacy and therapeutics. It is soluble, we have seen, in 16 parts of cold water and insoluble in alcohol, though very soluble in glycerin and fats. It has

been found that the addition of a small amount of sugar greatly increases the solubility of borax, and that it will also rapidly liquefy a solution of gum arabic which has become gelatinous from the presence of borax.

According to Dujardin, sodium borate, which as a general rule behaves like the alkalies, should not be associated with the salts of the alkaloids. In mixtures of this kind the patient is likely to take most of the alkaloid in the last dose, with harmful effect.

**SODIUM BORATE POISONING.**—The phenomena are the same as those caused by boric acid, the latter in fact being the toxic constituent of the salt.

Case of an infant 2 months old born strong and healthy which developed thrush a fortnight after birth. A mixture of borax and honey was applied, which relieved the thrush, but the child developed a liking for it, so that from two to three 4-dram (16 Gm.) boxes were used every week. The author describing the effects says that a progressive wasting had set in, and when he saw the infant there was a marked erythematous eruption on the palmar aspect of the hands and on the plantar aspect of the feet, with distinct desquamation between the toes and the fingers; well-marked urticarial eruption was present on the arms and forearms, but the region between the legs was notably free from eruption. There were tumefaction and tenderness of the abdomen and a raw, pinky redness of the lips, tongue, palate, and throat, with vomiting and looseness of the bowels. The face had a wizened look, the skin was soft and brownish, the eyes were bright, and the joints, especially the knees, tender, swollen, and somewhat stiff. There was no evidence of syphilis or other cause for the wasting and rash except the borax, of which the child had about 10 grains (0.65 Gm.) every day for six weeks. On stopping

the borax and confining the infant to breast milk, together with a little raw-beef juice, it appears to be recovering rapidly. McWalter (*Lancet*, Aug. 10, 1907).

**TOXIC EFFECTS OF SODIUM BORATE (BORAX) AS FOOD PRESERVATIVE.**—

The study of the toxic effects of boric acid submitted on page 591 applies also to borax. An experimental study of the influence of the latter, under the direction of H. W. Wiley, led him to the following conclusion:—

“The most interesting of the observations which were made during the progress of the experiments was in the study of the direct effect of boric acid and borax, when administered in food, upon the health and digestion. When boric acid, or its equivalent in borax, is taken into the food in small quantities, not exceeding  $\frac{1}{2}$  gram ( $7\frac{1}{2}$  grains) a day, no notable effects are immediately produced. The medical symptoms of the case in long-continued exhibitions of small doses or in large doses, extending over a shorter period, show in many instances a manifest tendency to diminish the appetite and to produce a feeling of fullness and uneasiness in the stomach, which in some cases results in nausea, with a very general tendency to produce a sense of fullness in the head, which is often manifested as a dull and persistent headache. In addition to the uneasiness produced in the region of the stomach, there appear in some instances sharp and well-located pains, which, however, are not persistent. Although the depression in the weight of the body and some of the other symptoms produced persist in the after-periods, there is a uniform

tendency, manifested after the withdrawal of the preservative, toward the removal of the unpleasant sensations in the stomach and head above mentioned.

“The administration of boric acid to the amount of 4 grams per day, or borax equivalent thereto, continued for some time, results in most cases in loss of appetite and inability to perform work of any kind. In many cases the person becomes ill and unfit for duty. Four grams per day may be regarded, then, as the limit of exhibition beyond which the normal man may not go. The administration of 3 grams per day produced the same symptoms in many cases, although it appeared that a majority of the men under observation were able to take 3 grams a day for a somewhat protracted period and still perform their duties. They commonly felt injurious effects from the dose, however, and it is certain that the normal man could not long continue to receive 3 grams per day.

“In many cases the same results, though less marked, follow the administration of borax to the extent of 2 grams and even of 1 gram per day, although the illness following the administration of borax and boric acid in those proportions may be explained in some cases by other causes, chiefly gripe.

“The administration of borax and boric acid to the extent of  $\frac{1}{2}$  gram per day yielded results markedly different from those obtained with larger quantities of the preservatives. This experiment, Series V, conducted as it was for a period of fifty days, was a rather severe test, and it appeared that in some instances a somewhat unfavorable result attended its

use. On the whole the results show that  $\frac{1}{2}$  gram per day is too much for the normal man to receive regularly. On the other hand, it is evident that the normal man can receive  $\frac{1}{2}$  gram per day of boric acid, or of borax expressed in terms of boric acid, for a limited period of time without much danger of impairment of health.

"It is, of course, not to be denied that both borax and boric acid are recognized as valuable remedies in medicine. There are certain diseases in which these remedies are regularly prescribed, both for internal and external use. The value which they possess in these cases does not seem to have any relation to their use in the healthy organism except when properly prescribed as prophylactics. The fact that any remedy is useful in disease does not appear to logically warrant its use at any other time.

"It appears, therefore, that both boric acid and borax, when continuously administered in small doses for a long period, or when given in large quantities for a short period, create disturbances of appetite, of digestion and of health."

**THERAPEUTICS.**—As an application to mucous membranes, because of its mildly antiseptic and soothing effects, borax in solution is very useful and often serves a better purpose than more pronounced astringents or local stimulants. Especially is this true of some of the lesser diseases of the eye and nasopharynx, the milder forms of **conjunctivitis**, certain forms of **rhinitis**, **ulcerative stomatitis**, etc. In the various milder forms of stomatitis in infants, borax and honey constitute a valuable household remedy. Sodium borate in camphor water secures a pleasant,

harmless, and grateful collyrium that may advantageously be employed, either alone or in connection with other remedies, in most inflammatory conditions of the eyes.

Sodium borate in solution may be employed topically to dissolve the pellicles of the epidermis joined together by sebaceous matter, thereby acting as a detergent; in **eczema** and other eruptions attended with **pruritus** due to the accumulation of products of the sudoriparous glands the salt is often most effective. Congenital **ichthyosis** is often benefited by washes of sodium borate.

In **erysipelas** Sevestre employs baths at 93.2° F. containing 16 ounces (500 c.c.) of sodium borate, which, he claims, lowers the temperature and tends to heal the eruption.

Both borax and boric acid have been recommended as injections in **dysentery**, but the solution should not be strong lest absorption and intoxication occur.

In **infantile diarrhea** daily irrigations of the larger bowel have been found most beneficial during the height of the disorder, borax, 1 dram (4 Gm.) to a pint (480 c.c.) of warm water, being employed.

That sodium borate has some action upon the central nervous system is apparent, but this is so ill understood that it is impossible to formulate any definite physiological basis for its internal administration. It has been tried in **epilepsy**, but is inferior to the bromides, while the chances of an eruption soon developing are greater. Borax has also been recommended for several nervous disorders, including **locomotor ataxia**, **paralysis agitans**, etc., but it is inferior to other remedies available.

Sodium borate is credited with a special affinity for the genitourinary organs. In some cases it relieves **uterine hemorrhage** with marked promptness; it has also proved very useful in **chronic cystitis** in 5-grain (0.3 Gm.) doses three times daily, coupled with washing out of the bladder with small quantities—a couple of ounces of a 2 grain (0.13 Gm.) to the ounce (30 Gm.) solution at 105° F. Stronger solutions, 5 grains (0.33 Gm.) to the ounce (30 Gm.), have also been found advantageous in **leucorrhea** and **gonorrhea**.

L. T. DE M. SAJOUS,  
Philadelphia.

**BRANCHIAL CYSTS AND FISTULAS.**—Whereas median congenital cysts and fistulas of the neck are derived from the thyroglossal duct, carrying epithelial cells with it from the floor of the mouth, the lesions more commonly termed branchial cysts or fistulas are lateral in position.

Insufficient obliteration of one of the branchial clefts, usually the second, in the embryo may, it is held, result in the production either of a cyst or of a fistula.

In the case of a cyst, both the internal and the external orifices of the pre-existing canal are regarded as having been obliterated, leaving a closed cavity lined with epithelium. In the case of a fistula, 3 possibilities exist. Either the entire canal may be open (complete fistula), resulting in the retention of a direct communication between the exterior and an interior cavity or channel, such as the pharynx or larynx; or the external orifice may have alone closed, leaving a fistula opening within; or, again, the internal orifice may alone have closed, leaving an external fistula. An opening without or within does not preclude the existence of cyst-like dilatations. Again, a complete fistula may become incomplete through closure of either orifice, and an incomplete (blind) fistula may become complete end.

Attention has been directed by F. Chris-

topher (Surg., Gyn. and Obst., Mar., 1924) to Wenglowski's studies of 78 embryos, numerous cadavers and 21 clinical cases of fistulas or cysts, which apparently disproved the branchiogenic theory of the origin of these lesions. The studies led to the conclusion that the branchial clefts or grooves in man are not open, and that the branchial apparatus cannot leave remnants in the neck below the hyoid, while the vestiges of the thymic duct, running obliquely from the lateral pharyngeal wall to the sternum, may change into a lateral cervical fistula or cyst.

According to studies by L. Baccarini (Arch. ital. di chir., ix, 279, 1924), however, the derivations from the thymopharyngeal and thyroglossal ducts do not cover all the cases of congenital neck cysts or fistulas. In one of his 11 cases the condition was ascribed to accidental inclusion of the ectoderm; in another to an inclusion of oral pavement epithelium in the thyroid anlage, and in a third to an unabsorbed remnant of cartilage of the 4th branchial arch. In 2 other cases the derivation was wholly obscure.

**Branchial cysts** have been classified as superficial or deep; as atheromatous (branchial dermoids), mucous, serous, or hematocysts (though not primarily blood-cysts); and, according to location, as auricular, parotid, submaxillary, sublingual, pharyngeal, tracheal, etc. Coplin has divided them into "branchial dermoids," showing the histologic characters of the skin plus an extra amount of lymphoid tissue, and "mucous branchial cysts," with a mucous lining resembling the oral, pharyngeal, or respiratory mucosa. The cyst wall may be smooth or irregular, and its thickness varies according to its content of lymphoid or fibrous tissues, sometimes attaining 1 centimeter. The presence of glands in the cyst wall has occasionally been reported. At times the cyst projects into the pharynx or esophagus, or it may extend between the trachea or larynx and the esophagus. Elongated projections of the cyst may exist between the muscles, vessels, and nerves of the neck, behind the hyoid bone or sternum, or along the auditory canal.

**Branchial fistulas** vary in extent from a mere capillary channel to a fissure of the entire neck. Their external orifices, while always anterior to the sternocleidomastoid



muscles, otherwise vary markedly in location, being now in the vicinity of the lower jaw, or in the temple, above the sternoclavicular joint, about the auditory canal, etc. In the midline the upper boundary of their distribution is the hyoid bone, and the lower limit, the suprasternal notch. In spite of this variability in the external opening, the route followed by the fistula is a definite one in that it passes at first over the deep fascia superficial to the sternohyoid muscle, then beneath the digastric muscle, finally terminating near the tonsil or entering the pharyngeal wall after crossing the carotid bifurcation and the glossopharyngeal and hypoglossal nerves (Gilman).

Branchial fistulas are nearly always unilateral and are said to be more frequent on the right side. Trélat is credited with the assertion that fistulous openings are 7 times as common as true cysts.

**SYMPTOMS.**—The cysts are, as a rule, discovered accidentally; a cyst of moderate size is likely to cause little or no discomfort. In a case reported by Coplin, a lump appeared on the lower jaw at the age of 33, and about two years later it began to enlarge rapidly and caused dull pain about the side of the face; at the time of operation it was 7 cm. long. Rickett's patient, however, was 16 months old and had a tumor the size of a bantam's egg which, one evening, enlarged suddenly to the size of an orange, and was successfully removed the next day. Large cysts may at times cause distress by exerting pressure on the larynx, pharynx, or blood-vessels, sometimes inducing dysphagia. The jugular vein may be displaced, and the carotid pulsations plainly felt, at times leading to a suspicion of aneurism.

The fistulas are usually manifest at birth, though occasionally they appear later as a result of the opening of pouches or cysts or through incomplete surgical removal. The external orifice is at times so small as to escape cursory examination, though frequently it is marked by a small area of scar tissue. Often little attention is paid to it unless the exuding secretion causes irritation of the surrounding skin or is sufficient in amount to prove annoying.

The discharge from the small skin opening is serous or seropurulent and frequently surrounded by a zone of eczema. In many

of the lateral and at times in the median fistulas or cysts the tract can be palpated as a distinct cord coursing vertically in the neck (Lipshutz).

**DIAGNOSIS.**—Differentiation of a branchial cyst from other tumors in the neck is often impossible, the true nature of the enlargement not becoming manifest until operative removal is undertaken. At times the contents of the cyst suggests pus or tuberculous caseous material rather than mucoid secretion. According to Coplin, however, certain minute features of the contents may prove of diagnostic utility, viz., the small number of leucocytes of the type usually found in pus, the presence of large mononuclear cells rich in perinuclear protoplasm, and the absence of necrotic material. Exploratory puncture might be availed of.

The secretion from a fistula is usually clear mucus. According to Sutton, where the fistula is complete and communicates with the esophagus or pharynx droplets of milk may escape during deglutition. Tracing the fistulous tract with a probe is seldom feasible and may puncture the wall or induce marked reflex symptoms. Where doubt exists, an opaque preparation, such as bismuth suspension, may be injected into the external opening and stereoscopic X-ray plates made, revealing the route of the fistulous channel. Injection of methylene blue just before operation is also a serviceable procedure for determining the course of a fistula.

**TREATMENT.**—The correct treatment of branchial cysts or fistula is **complete excision**, attempts at closure by injection of irritating solutions being attended with undue risk as well as marked uncertainty. Post-operative recurrence is obviated only by removal of every vestige of the branchial wall, however troublesome the necessary dissection may prove to be.

As pointed out by Christopher, no one operation for **excision** can be recommended to the exclusion of others, each having its merits according to the obstacles encountered. To identify the tract during dissection the best method is to inject methylene blue with a blunt needle until the dye appears in the pharynx. A single vertical or slightly oblique incision over the fistulous tract is probably best. It should start with

a small circular cut around the fistulous opening, which is then closed at once with a hemostat. Blunt dissection of the taut tract is best, carried on, if possible, under the posterior belly of the digastric muscle, with avoidance of the hypoglossal nerve. Upon reaching the pharynx, the freed tract should be divided between clamps about 2 cm. distal to the internal orifice and the proximal cut end cauterized. At this juncture the writer recommends the **von Hacker maneuver**: The proximal cut and cauterized end of the fistula is cautiously opened so as not to spill its contents, a probe bearing a ligature is passed through the fistula into the mouth, the ends of the ligature are made fast to the cut end of the fistula by transfixion, and the fistula is inverted into the pharynx by gentle traction on the ligature. The fistula is then ligated and cut off short, leaving in the pharynx a short stump which soon atrophies.

Where, as is occasionally the case, the fistula cannot be inverted even though wholly mobilized, its pharyngeal orifice is excised with a little of the adjacent mucosa and the latter closed with a purse-string.

In many instances the tract is so adherent from previous inflammation that it cannot be dissected out. In this event the **Koenig operation** should be employed, the free distal end being passed through the oral mucosa in front of the tonsil and sutured there. This transforms the fistula into a curved sinus with a pharyngeal opening at 1 end and a buccal opening at the other, all external discharge being thus done away with.

Report of 2 cases of branchial fistula and 1 of branchial cleft cyst. A girl, aged 13, had had a discharging sinus low down on the right side of the neck as long as she could remember. At times the discharge was clear, at others thick and yellow. For days at a time the opening apparently closed. Later it pouted at its central point, burst, and discharged a considerable amount of thick fluid, decreasing through several days. A few c.c. of a thin suspension of bismuth were injected into the opening and sealed in with gauze and adhesive. Stereoscopic plates demonstrated the exact relations of the tract from the skin opening to

its point of origin in the lateral wall of the pharynx near the tonsil. At operation the entire tract, still containing the injection material, was exposed through an incision medial to and paralleling the right sternomastoid, and extending from just below the angle of the jaw to and surrounding the opening. By exerting traction on a clamp the tract was readily brought into view, and the opaque material rendered its identification easy. It was removed by blunt dissection up to and beyond its point of origin in the pharyngeal wall, the dissection being carried well up to the base of the skull.

The cyst case was in a man of 25. The cyst was below the angle of the jaw on the right side, and was 10 cm. in diameter and fluctuated. It was shelled out by blunt dissection under 1 per cent. procaine anesthesia.

The second fistula case was in a girl, aged 16. A small opening on the neck had been noticed when she was 3 years old, and had discharged thin, greenish-yellow mucus ever since. By pressing on the neck above the opening she could force out at times half a teaspoonful of fluid. The treatment was similar to that in the first case. P. K. Gilman (Jour. Amer. Med. Assoc., July 2, 1921).

**MALIGNANT BRANCHIOMA.**—This is a primary malignant tumor of branchial origin. According to Lenormant, it is less rare than is generally supposed. One of his cases represented a malignant degeneration of a pre-existing branchial cyst. The other 3 had irregular tumors deep in the carotid or carotidosubmaxillary region which rapidly invaded neighboring structures. These tumors are usually of mixed nature and typically produce an indurated plaque, like cancer "en cuirasse." Lymphosarcoma progresses even more rapidly and is somewhat inflammatory in character. Cancer metastasis in a lymph-gland may be ruled out by careful study of the nose, larynx, and esophagus for a primary tumor.

**Treatment.**—The treatment of malignant branchioma is prompt and wide **excision**. If the supraclavicular fossa is already invaded the **clavicle** must be partly or wholly

removed. The sternomastoid muscle and internal jugular must be sacrificed, but preservation of the arteries is generally feasible. The lymph-glands of the region are simultaneously removed. The operative mortality has been given as 9 out of 60 cases. Early and rapid recurrence is almost the rule, but in rare cases apparent cure has been obtained. Radium and the X-rays have as yet afforded only doubtful benefit. S.

## BRIGHT'S DISEASE.

**ACUTE NEPHRITIS**, or **ACUTE PARENCHYMATOUS NEPHRITIS**, also termed sometimes, though infrequently, **Acute Bright's Disease**; **Acute Diffuse Nephritis**; **Exudative, Catarrhal, Tubal, Desquamative, and Glomerulonephritis of Acute Course**.

**DEFINITION.**—An acute inflammation of the kidneys, and either of a mild, severe, or grave character. It may be more or less diffuse in nature. Three varieties of acute renal disease have been described by Delafield under the term acute Bright's disease: (1) Acute degeneration of the kidneys; (2) acute exudative nephritis, and (3) acute productive nephritis. The following three forms are recognized by many other writers: (1) Acute tubular; (2) acute glomerular, and (3) acute diffuse nephritis, the latter combining the symptoms of the first two. Often these varieties cannot be distinguished clinically.

The term acute hemorrhagic nephritis is frequently used where hemorrhages in the kidney tissues or beneath its capsule are a prominent feature, with the cortex deeply mottled or hyperemic.

Bright's disease has also been divided, particularly by German writers, into *nephrosis* and true nephritis, the former term being applied more especially to exclusively degenerative processes in the kidney, acute or

chronic, unaccompanied by proliferative or exudative changes. Here again, however, distinction of the 2 groups from clinical data alone is often difficult.

Acute hemorrhagic nephritis in children is comparatively common. The authors regard it as one of the 2 main types of acute nephritis in children, the other being the more widely known parenchymatous or exudative variety. Pathologically, the hemorrhagic type is probably a streptococcal embolism of the kidneys, originating from some focus of sepsis elsewhere in the body. The prognosis is much more favorable than in other forms of acute nephritis, and chronic nephritis seldom follows. Wyllie and Moncrieff (*Lancet*, Jan. 16, 1926).

**SYMPTOMS.**—The onset is sudden, as a rule, but varies with the exciting cause of the nephritis. Chilliness, nausea and vomiting, pain in the back, and, within twenty-four hours, dropsy are seen in some cases. Children are subject to convulsions (uremic), and in severe cases adults are no less liable. Fever may be present, but it is neither constant nor high. The early appearance of edematous puffiness of the eyelids and face, and of pallor of the skin, is characteristic. Soon, and sometimes at first, a swelling occurs about the ankles and legs, and in severe cases dropsy involves the whole body. The scrotum, penis, or labia may, in such cases, become enormously distended, the skin presenting an almost translucent appearance. The blood-pressure is apt to be raised, especially in children.

There may occur a diffuse nephritis in which the glomeruli are primarily involved due to a general sepsis arising from some focus of infection. If this focus is discovered early and removed the nephritis may be recovered from completely, but in many cases its continued presence makes the nephritis progressive. The con-

dition is a true nephritis, as the lesions are typically inflammatory.

Three forms of the disease can be recognized: Acute, subacute and chronic.

One of the commonest focal infections, especially in the chronic types, is a chronic suppurative tonsillitis without material enlargement of the tonsils and due to a diplostreptococcus. W. Ophüls (Jour. Amer. Med. Assoc., Oct. 13, 1917).

A gallop sound was the first sign to call attention to the acute nephritis in cases observed by the writer. In a girl of 12, there was complete asystole when first seen; she was cyanotic, and almost pulseless. The gallop sound was due to an enormous dilatation of the heart. There was also bronchopneumonia, however, and the child seemed to be convalescing, when purulent pleurisy set in, ending in death. Ponce de Leon and Morquio (Arch. Latino-Amer. de Pediat., May-June, 1920).

Among 47 cases of acute nephritis, the writer observed both edema and red cells in the urine in 30. He rejects, therefore, the classification of acute nephritis into *acute glomerulonephritis*, with red cells, high blood-pressure, but usually no edema, and *acute tubular nephritis*, with degeneration of the convoluted tubules, edema, but absence of high blood-pressure and red cells. High blood-pressure seemed to be actually a favorable prognostic indication. In 7 cases the blood-pressure was 180 to 215 mm. Hg, and in only 4 was it below 130. The percentage of ultimate complete disappearance of albumin from the urine in his cases since 1917 was 94, whereas before 1914 it was 47. The high blood-pressure always returned to normal as recovery progressed. Sore throat was as frequent an etiologic factor in the "glomerular" as in the "tubular" type of case. Petrén (Ann. de méd., June, 1921).

The uniformly parallel course shown by hyperglycemia and hypertension in the author's cases of acute diffuse glomerulonephritis led him to conclude the high blood sugar and high blood-

pressure in this condition are due to the same causes. Hetényi (Med. Klin., June 30, 1923).

Often local symptoms are absent, as pain and tenderness in the lumbar region; they are never marked.

Micturition may be frequent and accompanied by a slight burning and vesical tenesmus, due to the concentrated urine.

In severe dropsy the tense, dry skin may become sensitive or even painful on pressure. Bodily movements are often painful and difficult in cases of marked anasarca. Uremia may be heralded by intense headache and backache.

In a report drawn up by the Medical Research Committee on War Nephritis, working in France, the writers describe the onset of the disease as usually insidious. The first indication in those doing heavy manual work was increasing shortness of breath; in sedentary workers, headache.

The edema present tended to clear up rapidly usually, with well marked diuresis and often heavy sweats. The albuminuria then usually improved considerably. Hyaline casts were the most abundant, granular next and epithelial last. A moderate rise of systolic blood-pressure was almost invariably present during the period of edema, falling to normal or below as the edema subsided. There was frequently a marked difference in the height of the morning and evening pressures, the latter being the higher. In most cases a definite hydremia could be demonstrated. Although cardiac symptoms were frequent, the only physical sign was a temporary enlargement of the heart to the left in 23 per cent. On discharge from hospital, however, the heart appeared normal. Chemical investigations showed no differences in kind between this and ordinary nephritis. The urea in the blood was usually increased, the chlorides variable. In convulsive cases which recovered, the blood urea was

not appreciably raised, whereas in a fatal case of uremia it was exceedingly high. De Wesselow and MacLean (*Lancet*, Sept. 14, 1918).

The form of uremia seen in acute glomerular nephritis in children is characterized by headache, vomiting, visual disturbances, delirium or coma and convulsions. It is always preceded by a steady rise in arterial tension and by visible but not necessarily marked edema. A steady increase of arterial tension is the most reliable indication of approaching uremia. Intracranial tension resulting from edema of the brain is probably the causative factor of the symptoms in this form of uremia. This is suggested by finding an edematous brain at necropsy and the relief afforded by treatment favoring a decrease of cerebral edema. Arterial hypertension is probably the result of increased intracranial pressure. Blackfan and B. Hamilton (*Boston Med. and Surg. Jour.*, Oct. 1, 1925).

A urinary examination is always necessary, as in mild cases the renal condition may be overlooked. There may be no further symptoms than a general malaise.

According to Janovsky, acute nephritis is frequently accompanied by a marked psychic depression which is of diagnostic value. Although the patient understands and feels as usual, and is free from headache, dizziness, and tinnitus, complete apathy and indifference to the environment become noticeable. There are no special symptoms and yet he does not feel well. The other symptoms of acute nephritis appear later.—Ed.

In a case of mercuric chloride poisoning, the anuria was accompanied by coma alternating with delirium, and there was 0.3 Gm. of urea per thousand in the blood. Death occurred the fifth day without edema or uremic symptoms. S. Pascual (*Medicina Ibero*, Jan. 18, 1919).

The urine in acute nephritis furnishes distinctive characteristics. The total

quantity passed in twenty-four hours is diminished, and may even be very scanty, varying from 5 to 25 ounces (150 to 740 c.c.). There may be suppression in cases of toxic origin, when an acute degeneration or necrosis of the renal epithelium occurs, and in the very severe exudative inflammations.

The specific gravity is early increased to 1025 or more, though later it may fall to 1015 or 1010. The color is darker than normally and is usually smoky red, or reddish brown, according to the amount of blood contained. A more or less abundant flocculent sediment appears on standing, if the normal morphological constituents are present in great quantity.

Some red blood-corpuscles and renal epithelium are found microscopically, together with the characteristic hyaline, blood, and epithelial tube-casts. The urine is acid in reaction, and on boiling throws down a thick, curdy precipitate of albumin, which varies in weight from  $\frac{1}{4}$  to 1 per cent. The urea is diminished.

The writers consider hemorrhagic nephritis a disease entity occurring during the course of an acute nephritis, and have seen 10 cases. The main diagnostic feature is the presence of a sediment consisting almost entirely of red blood cells with a rare hyaline or red-cell cast in the urine. The prognosis is usually good as to life, but most patients are left with some degree of nephritis. Treatment is not very satisfactory, but **prolonged rest** is most essential. O'Hare and W. G. Walker (*Atlantic Med. Jour.*, Feb., 1924).

Of 12 cases of acute nephritis in children,  $\frac{2}{3}$  of whom had markedly enlarged and chronically inflamed tonsils and adenoids,  $\frac{1}{2}$  showed massive hematuria, severe constitutional disturbance and slight edema. Smoky and dark concentrated urine was associated with less severe constitutional

symptoms. Oliguria was not a feature in any case. The functional tests for renal efficiency were of no prognostic or diagnostic value. The blood urea was temporarily raised in  $\frac{1}{3}$  of the cases. The large majority of patients had apparently recovered within a month from the onset. No uremia or death was encountered. Allison (*Pract.*, Mar., 1925).

The molecular concentration or osmotic pressure of the urine is usually reduced, so that the freezing point (cryoscopy) is  $1^{\circ}$  or less than  $1^{\circ}$  C. (instead of the normal  $1.3^{\circ}$  to  $2.3^{\circ}$  C.) below that of distilled water ( $0^{\circ}$  C.).

There may also be other symptoms during the course of acute Bright's disease, as those of hydrothorax, ascites, and hydropericardium, in cases in which great general edema is present. The first-named condition is bilateral and gives rise to dyspnea; the second increases the dyspnea by pressing the diaphragm upward, and the last impedes the heart's action. Strümpell described a form of pneumonia that sometimes develops in severe cases of acute nephritis,—a "stiff inflammatory edema,"—midway between lobar and broncho-pneumonia. There may also be edema of the conjunctivæ, soft palate, and larynx.

The pulse is often hard and tense, and, though slow at first, it may become accelerated later. Cardiac hypertrophy may be present in a slight degree. The aortic second sound is accentuated.

The large number of cases of acute nephritis observed during the World War permitted extended study of the cardiovascular complications of nephritis, which occurred relatively often. That the increase of blood-pressure was not very great was due to the youth of most patients. Its parallelism with the course of the nephritis, and its return to normal after cure of the

nephritis showed that the blood-pressure was related to the acute nephritis, and not due to pre-existing hypertension resulting from chronic nephritis, arteriosclerosis or other kindred conditions. Cases observed during the war proceeded either to complete cure, to persistence of simple albuminuria without alteration of renal permeability or blood-pressure, or, very rarely, to the establishment of chronic nephritis with or without hypertension. In the hypertension accompanying acute nephritis, the systolic pressure exceeded the normal by only 20 to 40 mm. Hg, while the diastolic pressure exceeded it by not more than 10 to 20 mm. Hg. This rise generally declined as the cases improved. In rare cases it did not wholly disappear, and some patients finally developed permanent hypertension. Low blood-pressure very rarely accompanied acute nephritis, occurring only when icteric intoxication co-existed. The hypertension is probably an endocrine-sympathetic reaction produced either by toxins insufficiently eliminated, or constituting a defense reaction tending to increase renal secretion. C. Lian and Hague-nau (*Arch. des mal. du cœur*, Aug., 1924).

Epistaxis appears occasionally, and subconjunctival hemorrhages sometimes follow unwitnessed uremic convulsions. Dryness and uremia of the skin form a constant condition. Uremic manifestations may supervene at any period in the disease, appearing early in the most severe cases, with intense headache and backache, vomiting, and convulsions.

The above may be considered a description of the common form of acute nephritis resulting from exposure; the clinical course differs somewhat in other cases. Occurring as a complication of the infectious fevers, except scarlatina, acute nephritis may be characterized by the very slight degree, or even by the absence, of dropsy. Albuminuria, hema-

turia, anemia, and uremia mark the graver affections—*acute tubular nephritis*. In scarlatinal nephritis, an illustration of *acute glomerular nephritis*, anasarca is common, and a slight edema, at least, is quite constant. Mild affections show simply a slight quantity of albumin and a few hyaline casts, indicative of the parenchymatous degeneration. The typhoid state may follow the subsidence of the acute toxic symptoms in cases of *degenerative nephritis* due to mineral poisoning; this is marked by prostration, muscular twitchings, stupor, coma, and death. Hematuria may be pronounced in the so-called nephrotyphoid condition, in which typhoid fever begins with marked symptoms of acute nephritis.

Report of 15 cases, 9 fatal, of an association of severe icterus with nephritis. Characteristic was the initial severity and rapid course. There appeared to be no element of contagion nor epidemicity. The symptomatology is strikingly uniform. The patients are stricken suddenly with fever, chills, headache, vomiting, diarrhea, and oliguria (fever may be absent). There was nervous adynamia and a stuporous state suggesting typhoid. There may be neuritic pain in the lower extremities, precordial or epigastric anxiety, and an anxious facies. Icterus may appear in a few hours or a few days, and is of the classic choluric type; the stools are, as a rule, not decolorized. The participation of the liver is shown by hemorrhages, which in some cases appear in crops. There is cessation of fever after several days. Albuminuria shows no typical behavior. The outcome depends, however, on the activity of the kidneys; if diuresis can be established the patient has a better chance of survival. Merklen (*Revue de méd.*, Mar., 1916).

The *nephritis of pregnancy*, as a rule, is gradual in its onset. The albumin

increases in quantity from month to month, reaching a high percentage during the eighth and ninth. Some hyaline casts are found, but otherwise there are few morphological elements. Red blood-corpuscles rarely may be seen in the urine. Up to the time of delivery the danger of eclampsia is constant, but recovery is rapid in uncomplicated cases after the birth of the child.

In *acute productive nephritis* in which there is a tendency to the formation of patches or wedges of fibrous tissue, there is a higher fever, with cerebral and circulatory disturbances of a typhoid nature, as well as anemia, dropsy, and a highly albuminous urine, even though there be no blood-corpuscles and few casts. Dropsy is most marked in the legs. There are a progressive and rapid loss of flesh and strength, dyspnea, vomiting, diarrhea, and convulsions or coma ending in death. Milder cases last from two to four weeks, and apparently recover; albumin and casts persist, however, until another and a similar attack occurs after an interval of weeks or months. Thus, the first acute attack is subject to chronic recurrence, until a fatal seizure takes place.

In 26 cases of a so-called rheumatic inflammation of the eyes, more or less nephritis was found in all except 1, and in this case only one examination of the urine had been made. In 7 instances the renal inflammation was apparently only parenchymatous. Austin O'Malley (*Amer. Med.*, Nov., 1911).

The eye changes in trench nephritis were studied by the author. Almost invariably marked retinal congestion, with large pulsating veins, was present. Some weeks later, definite nerve swelling, accompanied by patches of retinal exudation, was seen. The spots of exudation were generally near the disk and in the

**macular area.** Hemorrhage was not common. Small areas of edema were noticed, especially along the veins. The condition is probably an acute congestion resulting from some specific toxin. The exudation probably clears up in most cases. The condition is probably allied to the acute retinitis of pregnancy, scarlatina, and acute uremia, and should not be confounded with the retinitis of chronic kidney inflammation. Kirk (Brit. Med. Jour., Jan. 5, 1918).

**DIAGNOSIS.**—Acute Bright's disease can hardly be overlooked when the urine is carefully examined chemically and microscopically. The eclampsia of pregnancy can, however, be recognized only by repeated examination of the urine, especially during the last months of pregnancy. Acute nephritis should be suspected, and the urine examined, in every case showing pallor of the skin and puffy eyelids, whether general prostration of the health is apparent or not.

Among 50,000 soldiers, the total percentage of albuminuria (unaccounted for by pus, spermatozoa, blood, etc.), was about 5 per cent. The average of urines found to contain casts was 1.87; of this number 0.84 per cent. had definite epithelial casts, while in 1.03 per cent. hyaline casts only were found. Out of 161 patients returned as nephritis or albuminuria only 28 had albuminuria before going to the front. MacLean (Brit. Med. Jour., Jan. 25, 1919).

The typical symptoms of acute exudative nephritis, as commonly seen when the condition is due to cold or occurs in scarlet fever, are the following: Headache, restlessness, muscular twitching, nausea and vomiting, a tense pulse, moderate fever, dropsy, and anemia. Tube-casts and albuminuria are constant. It should be borne in mind that slight albuminuria occurring in the course of pregnancy or during any of

the fevers, without casts, is not a true nephritis, although the latter may be a more or less remote consequence of the glandular degeneration of the renal epithelium associated with the febrile albuminuria. In addition to the presence of albumin and hyaline and cell-casts, however, a diminished quantity of sooty-looking urine and the discovery of red and white blood-corpuscles will render the diagnosis positive. The history of the case and the causal factors are also to be considered.

At times a diagnosis of the subvariety of nephritis present can be made. In acute *tubular* nephritis, often the result of an intoxication, less commonly of a severe infection or chilling, the urine is scanty, turbid and often reddish-brown, with sediment consisting largely of kidney epithelium and casts. Edema is lacking, and jaundice, myocardial weakness, etc., may reveal the effects of the toxic agent on other viscera. In acute *glomerular* nephritis, the urine is likewise scanty, but there is a large amount of albumin, with but few or no casts or kidney cells; furthermore, general edema is usually present.

The value of *renal efficiency tests* in nephritis in children was studied by the writer, who reached the following conclusions: (1) At the onset of the disease they do not give any more definite evidence of the severity of the case than do the clinical symptoms; (2) they do not give any indication as to the ultimate results; (3) during the course of the disease they merely corroborate the clinical symptoms; (4) they do not help in deciding if the case is cured, and (5) they are not of any help in differentiating between acute, subacute and chronic nephritis. E. Crawford (Glasgow Med. Jour., Feb., 1924).

**ETIOLOGY.**—Acute nephritis more often appears before than after the



middle time of life, though it may occur at any time. Males are more often attacked than females.

Occupations necessitating exposure to cold and wet offer special predisposing conditions. The long-continued use of alcohol will also, as a rule, prove a predisposing cause of acute Bright's disease.

Among the exciting causes of acute diffuse nephritis are:—

1. Those acting on the skin, as cold, dampness, extensive burns, and chronic skin diseases. It is often difficult to determine the relative influence of alcoholic excesses and the exposure incident thereto. It is likely that in most cases the exciting cause is the cold acting upon the individual in his exposed and maudlin condition. Acute nephritis may also be caused, at times, by exposure to cold and wet apart from and in the absence of alcoholic indulgence; in such cases it is to be presumed that there is an inherent weakness of the kidneys, or a susceptibility rendering these organs the vulnerable point in the system.

Report of 2 cases of traumatic nephritis in young women who had been kicked in the abdomen and trampled upon. In the first, the acute nephritis soon subsided. In the second case the urine contained much blood from the first, and urination was not painful as in the first case. By the end of a month there was no blood but many casts and much albumin, and on re-examination 10 months later, the urine showed unmistakable evidence of chronic nephritis. M. Castañeda (Cronica Med., May, 1917).

The physiological toxic agents embrace the poisons of the acute infections; in a majority of cases, however, scarlet fever is the primary affection. Usually the nephritis appears during the second or third week of convalescence,

though it may supervene at the height of the disease.

As stated by Hutinel, the nephritis of childhood, aside from scarlet fever, may be caused by any of the infectious diseases. Among these are measles, diphtheria complicated with a mixed infection, severe infections of the tonsils and pharynx that are not caused by the Klebs-Löffler bacillus, intestinal intoxications, appendicitis, etc. In some cases the child has had scarlatina some years before, and the kidneys have been impaired, and thus form a point of least resistance for new infection. Under such circumstances exposure to cold has an important etiological bearing.

In *acute glomerulonephritis*, the cause is nearly always some acute infectious process, usually streptococcal. The bacteria gain access to the blood, and the injury is probably produced by the direct action of their bodies on the glomerular epithelium. Degenerative, exudative and proliferative types of glomerular inflammation occur; the proliferative are chiefly responsible for permanent glomerular damage. The great majority of chronic cases do not, however, begin as frankly acute nephritis. *Acute interstitial nephritis* is seen most commonly in scarlet fever, and rarely in other infections. E. T. Bell and T. B. Hartzell (Arch. of Int. Med., June, 1922).

In 102 cases of glomerular nephritis in children, infections were usually responsible, and comprised the following: Chronic upper respiratory infections, 33 cases; scarlet fever, 26; acute upper respiratory infections, 12; acute mastoiditis, 5; pneumonia, 10; diphtheria, 4, and chronic sinus infections, 4. Deaths in this group numbered 21, viz., uremia, 10; pneumonia, 4; sepsis, 4; cardiac failure, 2, and pertussis, 1. In glomerular nephritis the infection is usually an acute self-limited streptococcal infection; when it subsides, the patient recovers. Of 28 cases of tubular nephritis, 13 died. Sinus infection was certainly the cause of the disease in 13 cases, and probably so in 4 others. S. W. Clausen (Atlantic Med. Jour., Jan., 1926).

Stress laid on gastrointestinal toxemia as a cause of nephritis. The author refers to 3 cases in which the arresting feature was an abnormality in the gastrointestinal canal. The first had pyorrhea, dilatation of the stomach, with a history of gastric inflammation, and the tongue bore evidence, from the enlargement of the papillæ, that there was an abnormal condition of the ileum. The second had septic ulcers in the mouth and on the tongue, and a constant discharge of purulent material from the nose, which in all probability was the cause of the septic condition in the upper part of the alimentary canal. The third case had equally striking gastro-intestinal symptoms, with definite physical signs pointing to a gastro-intestinal cause. In a fourth case of nephritis there was enormous distention of the colon and a large amount of ascitic fluid. The patient had suffered for 2 years from severe and continuous diarrhea, with foul-smelling motions. A posterior colostomy was done and the symptoms were greatly relieved, but the patient later died from sudden heart failure. In each of these cases the presence of toxemia was demonstrated by a pronounced *tache cérébrale*. William Watson (Glasgow Med. Jour., July, 1918).

2. Acute nephritis may also be the result of other of the infectious fevers (small-pox, typhus, typhoid, relapsing fever, cholera, diphtheria, yellow fever, measles, chicken-pox, erysipelas, septiopyemia, acute lobar pneumonia, cerebrospinal meningitis, dysentery, acute articular rheumatism, and tuberculosis; syphilis is rarely a cause).

Study of 28 cases of pneumococcal nephritis in children, 1 of which is original. The writer distinguishes 3 varieties of pneumococcal nephritis: 1. Albuminuria in the course of pneumonia, which is a mere episode in an infectious disease without any special gravity. 2. A severe form characterized by the usual symptoms of acute

nephritis. In the great majority of cases the pulmonary lesion is a bronchopneumonia. This is the most frequent variety, since 22 of the 28 cases were fatal. 3. A mild form affecting older children and associated with lobar pneumonia. Anatomically pneumococcal nephritis is characterized by lesions of the renal parenchyma, the convoluted tubules being principally affected. V. Schmarine (Brit. Jour. of Dis. of Children, Sept., 1911).

Nephritis occurs often enough in recently acquired syphilis to justify reduction of salt and a milk-vegetable diet during the first stage. In a case of nephritis in tertiary syphilis, no benefit followed 3 weeks of dieting, and when mercurial and iodide treatment was pushed, in 2 weeks there were no further signs of dropsy or headache. In a case of hypertension complicating the nephritis, specific medication increased dyspnea and caused symptoms of lung congestion. After repose, restriction to milk, wet cupping and small venesection, the man was enabled later to stand cautious resumption of specific treatment. M. del Sel (Prensa Med. Argentina, Oct. 30, 1917).

The term trench nephritis is a misnomer, for it is unnecessary to have lived in the trenches to suffer the affection. In most instances the individuals had previously been robust and without ailment. A few had had an antecedent sore throat or bronchitis. Edema was commonly the earliest manifestation. Headache was not uncommon and nocturnal dyspnea occurred in 78 per cent of cases. A rise in blood-pressure was noted in about one-half the cases. In a number of instances the nephritis was recurrent, the individual giving a history of previous illness having no relation to the military conditions. In the series reported 6 per cent. had convulsions. Only 1 case died, a recurrent one with small granular kidneys. The condition probably has its basis in infection and is of the nature of a glomerulonephritis. Ru-

dolph (Can. Med. Assoc. Jour., vii, 289, 1917).

History of recent tonsillitis, acute rheumatism, or severe chilling noted in a large proportion of cases of acute nephritis in soldiers in active service; in others there was pyorrhea, otitis or furuncles, but in fully 50 per cent. of the cases its origin was obscure, notwithstanding the more or less epidemic character. There is much to sustain the assumption that war nephritis is a hitherto undescribed infectious disease. It seems to have been known in Russia in times of peace, and also during preceding wars. The blood-vessels bear the brunt of the attack, and the vascular lesions are apt to retrogress completely with early and complete recovery. Privations and vermin probably are etiological factors. Ceconi (Riforma Medica, Jan. 26, 1918).

Report of 160 cases of war nephritis. The chief predisposing factor was age, five-eighths of the patients being over 30. The season appeared to make little difference. In 16 cases there was a history of previous renal disease; in 12 of scarlet fever, and in 5 of diphtheria. The disease is probably of infective origin, since the first stages are often marked by fever and frequently associated with influenza, bronchitis, trench fever, gastroenteritis, boils, tonsillitis, or other infective condition. In addition, there are symptoms of irritation of the urinary tract similar to those caused by the *B. coli communis*, and the condition is very similar to scarlatinal nephritis. The disease cannot be ascribed to any small agent, and the absence of epidemiology would seem to negative the assumption that it may be due to an infective agent as yet undiscovered. The greater incidence in the army as compared with civil life is explained by (a) sensitiveness of the renal tissues, due to fatigue and exposure, (b) greater liability to the entrance of infective agents into the blood-stream and thence into the kidneys.

The diastolic interval was shortened in about 50 per cent. of cases. More frequent still was a ringing accentuated second sound at or near the apex. Pulmonary physical signs may be bronchial or basal. Twelve cases manifested uremic symptoms; 4 of these died; 2 of the deaths were due, however, to concurrent bronchitis. As a means of diagnosis, the author recommends the salicyl-sulphonic acid test. The mortality in the series was 3.75 per cent. The most dangerous type is that in which intense nephritis occurs with severe bronchitis. C. F. Coombs (Lancet, Apr. 6, 1918).

Five cases of acute nephritis due to typical impetigo contagiosa. The condition may be just as severe as that following scarlatina. The risk of nephritis, even in efficiently treated cases, is quite as great as in scarlatina, and impetigo explains many obscure, sudden and acute cases of nephritis in children. Possibly many cases of so-called "trench nephritis" in soldiers are the result of an impetiginous pediculosis or scabies. Stiell (Pract., Apr., 1918).

There is a type of acute infective nephritis involving multiple, small or large areas, which, as a rule, proceed to abscess formation. These areas are for the most part situated in the cortex. The infection is usually unilateral. The lesions may resolve or leave the kidney so damaged that complete recovery is impossible and may serve as a foci for further infection. The commonest infecting organism is a member of the *Bacillus coli* group, but other organisms, as the staphylococcus and *B. typhosus*, may produce similar lesions. The infection is in most cases probably lymphatogenous or hematogenous, and in some cases of *Bacillus coli* infection some abnormal condition of the gastro-intestinal tract, seems to play a distinct part. There are frequently no demonstrable lesions of the genitourinary tract. Treatment may be palliative, but operation may be necessary. If nephrec-

tomy is performed early the prognosis is good. Campbell and Rhea (Surg., Gynec. and Obst., Dec., 1918).

Case of *typhoid nephritis* in a young woman. The paratyphoid B infection suggested ordinary typhoid fever until, during the 2d week, edema and tachycardia developed, with tube-casts. Complete recovery followed. Chalié and Desjacques (Paris méd., June 2, 1923).

Case of convulsions with albuminuria and hypertension in a young man, in whom a chronic infection of the tonsils and nasopharyngeal region was the apparent cause, complete recovery following **tonsillectomy**. Léon-Kindberg and Bloch (Bull. Soc. méd. des hôp. de Paris, Oct. 10, 1924).

Three cases in which an acute glomerular nephritis appeared about 2 weeks after recovery from a peritonsillar abscess. J. G. Smith (Okla. State Med. Assoc. Jour., Nov., 1925).

Case of *acute syphilitic nephritis*, developing during the secondary stage of untreated syphilis. No other cause for the condition could be found. A. J. Hood and F. D. Murphy (Amer. Jour. of Syph., Jan., 1926).

It may also supervene as a primary condition, and the brunt of the attack may be sustained either by the kidney, rather than by any other part, or by the organism as a whole, as in the fevers. Mannaberg has described such cases, and has demonstrated the presence of streptococci in the urine.

3. Chemical toxic agents include turpentine, cantharides, carbolic and salicylic acids, potassium chlorate, iodoform, the mineral acids, and inorganic poisons, such as phosphorus, arsenic, mercury, and lead. Acute renal inflammation may be caused by the excessive ingestion of highly acid, spiced, or adulterated foods (as from salicylic acid and lead chromate). Balsam of Peru, used too freely in the external treatment of scabies, has caused a number of cases.

In experimental nephritis, chromium salts, corrosive sublimate, and uranium nitrate are, as shown by Hedinger and Takayasu, toxic agents which attack first the tubular epithelium and leave the vessels at first undamaged. In the early stages of this tubular nephritis, salt solution and caffeine, when ingested, cause an increase in the volume of the kidney with diuresis. Cantharidin and arsenic, on the other hand, attack primarily the blood-vessels of the kidney and set up a vascular form of nephritis. In the early stage of this vascular nephritis, neither salt solution nor caffeine produces any increase in the volume of the kidney or diuresis. The ability of a substance to produce diuresis seems, therefore, related to the ability of the blood-vessels of the kidney to react to stimuli.

Experimental nephritis produced in dogs with cantharidin, arsenic, diphtheria toxin, and potassium chromate. There was retention of the non-protein nitrogen, urea nitrogen, and chlorides in the blood, and in addition, acidosis. Some dogs showed symptoms resembling uremic coma. Sodium bicarbonate, given by stomach tube, diminished the acidosis. In the milder grades of the disease, the action of the same amounts of poison was variable in different animals. Kingo Goto (Jour. Exper. Med., Mar., 1918).

4. Pregnancy may act as a cause of acute nephritis (*gravidarum*). In such cases it usually appears in primiparæ, in the last months of gestation, and is probably the result of renal engorgement due both to mechanical pressure and to nutritive disturbances in the kidney, owing to the altered blood-condition.

5. Latent chronic nephritis may form the cause of a manifest acute nephritis.

Christensen has recorded details respecting the urine findings in 10 football players, 12 wrestlers, 27 athletes after their exercises, and a number of others, all showing that the urine sediment after these exertions resembles the sediment in severe nephritis. Half an hour's wrestling by a

robust and healthy individual will bring fat into the sediment of the urine just as is observed in chronic nephritis, but evidently it is merely the result of the changes induced in the circulation.

**PATHOLOGY.**—There is a considerable variation in the anatomical changes in and the appearance of the kidneys, according to the degree of involvement. Between the very mild and grave cases there is an intermediate series of continuously more marked pathological changes dependent upon the amount of poisonous material circulating in and eliminated by the kidneys, as well as upon the intensity and duration of its toxic action.

There may be no macroscopic change in the mildest cases. As a rule, however, the kidneys are slightly enlarged, swollen, and somewhat softened, though these conditions are more evident when the interstitial exudation is abundant and inflammatory edema is evident. On section the organs may appear red and congested or they may be pale and mottled. In the former case hemorrhages may appear beneath the capsule (acute hemorrhagic nephritis); it is more usual, however, to see red, hyperemic patches alternating with opaque and whitish portions, both on the outer and the cut surfaces. Especially is the cortex swollen, turbid, and pale or slightly congested in the mildest cases; in severe attacks it is deeply mottled (red and pale glomeruli) or hyperemic. The surfaces are smooth and the capsule non-adherent. The pyramids usually show an intense-red color.

In the very mild cases, already referred to, changes may be noted microscopically that are not visible to the naked eye, there being simply a cloudy swelling or a granular (parenchymatous) degeneration of the epithelium of the Malpighian tufts, Bowman's capsule,

and of the uriniferous tubules of the cortex. In the absence of exudative changes in the interstitial tissue, however, this cannot be called true acute nephritis. The acute parenchymatous degeneration may be limited almost exclusively to the glomeruli, as in some cases of scarlatina, and from this fact has arisen the term *glomerulonephritis*. The nuclei are either swollen or absent; the cells are swollen, opaque, and irregular in shape, and the cell-contents are granular (albuminoid or fatty). The death of the cells—owing to coagulation necrosis or disintegration, desquamation, and hyaline degeneration of masses of the cells in the tubules—marks a further stage in the process. Acute degenerative changes are frequently found in the acute infectious diseases, or when inorganic poisons have been introduced into the body. In phosphoric poisoning there may be an actual fatty degeneration of the epithelium, either proceeding from the cloudy swelling or occurring as an independent development. In severe cases a rapid necrosis of the cells is also met with.

In glomerular nephritis there is marked variability in the macroscopic features of the organ, owing to differences in the amount of blood contained in its various component structures, the degree of infiltration with serum, and the extent of fatty degeneration. Upon incision of the kidney a clear differentiation of the cortex and medulla is apparent, with darkness of the pyramids. Microscopically there is found increased length and width of the capillary loops of the glomeruli, with increase of cells within the loops and an appearance of pallor. The capsular space ranges as to its contents from coagulated albumin to red cells and leucocytes or shed epithelium. The proximal convoluted tubules related to the most markedly diseased glomeruli may exhibit granular and fatty degeneration. If the condition of so-called "nephrosis" co-exists, the associated degenerative changes

in the tubules are manifested in extensive granular and fatty degeneration of these canals.

There may be fairly extensive lesions in the kidneys without corresponding evidence of damage of renal function; this is because of the reserve function of these organs. *Focal embolic glomerulonephritis*, which is a common complication of infective endocarditis, is featured by the appearance of minute plugs of thrombus in the glomerular capillaries. *Acute interstitial nephritis*, which occurs as a complication of scarlet fever and streptococcal infections, is characterized by the development in the stroma of the cortex of discrete areas of infiltration with inflammatory cells. In these areas the glomeruli and tubules undergo complete atrophy and disappear, but usually a large proportion of the renal tissue remains undamaged between the foci, and consequently definitive renal symptoms are absent.

As for *subacute nephritis*, in one type (the *nephrosis* of Volhard and Fahr), the changes are almost limited to the tubules, and comprise edematous swelling of the epithelial cells, fatty and hyaline droplet degeneration. In the second type, the glomeruli show lesions which are the logical outcome of those of acute glomerulonephritis. Sometimes these lesions are confined to the tufts, and consist of hyaline thickening of the capillary walls with narrowing and persistent excessive cellularity of the capillary lumina; with this there is late capsulitis, exhibiting laminated fibrous overgrowth in the situations where exudate and catarrh occur in the initial stage. J. S. Dunn (Glasgow Med. Jour., Feb., 1924).

True acute nephritis exhibits not only changes in the parenchyma (epithelium), but also an inflammatory exudate between the tubules, consisting of serum, leucocytes, and red blood-corpuscles. In some places the kidneys show only a slight cellular infiltration of the intertubular tissues. In others the interstitial tissue is swelled by the

coagulated serofibrinous exudate, many leucocytes, and some erythrocytes, besides the desquamation of necrotic epithelial cells and the presence of hyaline casts in the tubules. The inflammatory exudate collects, also, in the Malpighian bodies and tubules. The tubules may be dilated and choked with degenerated cells, or, more frequently, the straight tubules are clogged with hyaline casts. The lining epithelium, especially in the convoluted portion of the tubules, is often flattened. The white blood-corpuscles infiltrating the stroma of the kidneys are collected in foci in the cortex, and not, as a rule, equally diffused.

Marcuse has explained the rise of blood-pressure in nephritis in the following way: The renal inflammation causes an obstruction to the flow of blood in both kidneys, and as a result of this there is an increased flow of blood in the inferior suprarenal artery, which is a collateral of the renal artery. The consequent hyperemia of the adrenals would lead to their hypertrophy, and with this would come an increase in production of adrenalin, causing a rise of blood-pressure.

Glomerulonephritis was produced experimentally by repeated intravenous injections of *Staphylococcus aureus* toxins in rabbits which had been given a preliminary injection of uranium nitrate. Similar lesions resulted from intravenous use of *B. mucosus capsulatus*. A single large injection caused an acute hemorrhagic nephritis in 6 hours. By reducing the dosage and giving it repeatedly over a long period, the writer was able to produce the pictures of subacute and chronic nephritis. In the former the most striking change was degeneration of the tubular epithelium. In the latter the kidney under the capsule presented a granular surface and the microscopic picture was that of diffuse chronic nephritis. Major (Jour. Med. Research, xxxvii, 125, 1917).

In a study of the bacteriology of the urine in nephritis in 29 cases, 20 of

which were chronic and 9 acute, the writer obtained cultures of streptococci in 5 cases. In 10 cases, a feebly Gram-positive organism was found, and in 5, a spore-bearing organism. Other organisms found were: *Staphylococcus aureus*, 6 times; an anaërobic *S. aureus*, twice; *S. albus*, once; *B. coli*, 3 times, and *Diplococcus crassus*, once. Only 2 of the specimens were sterile. W. E. Cary (Jour. of Infect. Dis., June, 1924).

The outlines of the individual capillaries are lost, and the glomerular epithelium of the capsule—especially that covering the inside of the capillaries of the tufts—is swelled and opaque. New epithelium appears in most instances of diffuse exudative nephritis, and a restoration of the glomerular function occurs. According to one view, in the productive variety of acute diffuse nephritis, however, certain lesions are more permanent in character from the outset in the glomeruli and stroma, and hence the increased gravity of the disease. Superadded to the usual exudative condition are the following changes: (a) a growth of the cells lining the capsules, such as to form a mass that compresses the tuft, “and leading, finally, to obliteration of the vessels and fibroid glomeruli”; (b) a growth of the connective tissue parallel to, and surrounding, one or more arteries having thickened walls, and forming more or less numerous and regular strips or wedges in the cortex. The new tissue between the tubules is, in the more intensely acute cases, largely cellular; in those of a subacute type it is relatively dense and fibrous.

Pleural, pericardial, and peritoneal dropsy, as well as anasarca, are also found in those dying of acute Bright's disease. Meningitis, cerebral edema, and lobar pneumonia are also sometimes seen *post mortem*.

**PROGNOSIS.**—A case of ordinary exudative nephritis following exposure to cold and wet runs a course varying from a few days to three or more weeks. There is a steady diminution of the albuminuria, which finally disappears together with the casts, while the daily quantity of lighter urine and the daily excretion of urea increase. The character and intensity of the renal inflammation, and the primary disease or causative conditions largely determine the prognosis. Scarlatinal nephritis gives much less hope of recovery than does nephritis due to exposure to cold after alcoholic excesses. Recovery usually takes place easily after the acute parenchymatous degeneration that accompanies diphtheria, typhoid, and other infectious fevers, as well as pregnancy. In acute yellow atrophy, however, and in yellow fever, cholera, severe phosphoric or mercurial poisoning, death may occur from the intense and widespread necrosis of renal epithelium. The dropsy and albuminuria gradually diminish in favorable cases of ordinary exudative nephritis, while the color of the skin and the quantity of urine and urea increase; so that recovery is established in from three to six weeks. The albumin may persist for some time after the disappearance of the dropsy, and then gradually disappear; rarely, however, in unfavorable cases, albuminuria may continue and the affection become chronic parenchymatous nephritis, even after the dropsy has disappeared.

A small amount of albumin may be present in grave renal lesions, and, on the contrary, a large quantity of albumin may not necessarily mean a fatal prognosis (albuminuria from excessive fatigue). Again, edema may be met with in parenchymatous nephritis, while absent in the interstitial form, in which it appears only

in consequence of cardiac insufficiency. The cardiac and vascular symptoms are of very great importance in forming an opinion about the prognosis. Signs of cardiac debility betoken clearly an approaching danger. Alterations in the retina are of bad prognostic omen; out of 100 cases of albuminuric retinitis Bull followed up 86, 57 died during the first year, 12 during the second, and 17 later. Phenomena of uremic intoxication are not always grave. In acute nephritis the patient may recover after delirium and even convulsions. Headache that resists treatment is a bad indication; if accompanied by vertigo, stupidity, and insomnia, it indicates an approaching explosion of grave symptoms. Dyspnea and asthmatic attacks may last for years, while Cheyne-Stokes respiration appears usually during the last weeks of life, and occasionally during the last months.

Acute nephritis presents a number of serious and often dangerous symptoms. Among these are severe general edema, dropsical effusions into the serous sacs (as hydrothorax), uremia (especially when beginning with cerebral manifestations, as convulsions or coma), and, finally, inflammation of the internal organs, as pneumonitis, pleuritis, pericarditis, peritonitis, and meningitis. Recovery is quite common in cases of marked general dropsy in the absence of uremia. Suppression of the urine, however, if it lasts more than twenty-four or forty-eight hours, is usually a fatal symptom. In those cases, also, in which the nephritis has a productive character, the prognosis is unfavorable, though life may, in some cases, be prolonged for several years.

Study of acute nephritis in children in respect to prognosis in later life in 106 persons who had had acute nephritis before the age of 15, and 50 whose acute nephritis occurred between the ages of 15 and 20. The intervals since the nephritis ranged from sixteen to twenty-three years. The nephritis occurred in connection

with some acute infectious disease in all but 27 in the first group, but in none of the 40 individuals the writer was able to re-examine were there any signs or symptoms suggesting that the kidneys were below par. The same negative findings were observed in most of the 16 relocated and re-examined in the group of 50 older patients. Ernberg (*Nordiskt med. Arkiv*, vol. xlv, No. 2, 1912).

In very severe acute nephritis the renal function during the early stages is much better than the actual state of the kidneys would seem to warrant. This the author ascribes to the stimulation to which the kidneys are subjected at the outset. With the subsidence of the inflammation, however, the renal function tends to fall to a low level. Thus in 1 case an extreme and prolonged impairment in the rate of urea excretion first appeared at a time when the patient was beginning to show marked general improvement. Simultaneously the rate of phenolsulphonaphthalein excretion was impaired, but the blood plasma chloride and the chloride threshold returned practically to normal. This is the critical period in acute nephritis; during the resulting prolonged rest of the kidneys great care must be taken not to overstrain the exhausted function. Theophylline probably acts in part by lowering the chloride threshold; the chlorides are thereby allowed to pass out of the blood plasma, and water follows. E. H. Mason (*Arch. Internal Med.*, Feb., 1918).

Studying the prognosis of war nephritis in 50 patients, the authors found almost all cases to show after a period of 3 months a trace of albumin, a few granular and hyaline casts, red blood cells, and pus. The chlorids and urea were about normal. Nocturnal micturition was present in nearly 40 per cent. of the cases. Many still complained of dyspnea, slight headache, and pains across the lower part of the back, and a few developed slight transient return of edema. The patients were usually



well nourished and not anemic, with striking absence of the pale countenance of the ordinary nephritis of civil life. In over half the cases there had been, at the onset, acute catarrh of some part of the respiratory passages, most frequently a bronchitis. A. R. Robertson and others (Can. Med. Assoc. Jour., Mar., 1918).

Little prognostic value attaches to the various renal functional tests, according to Rowntree, in view of the rapidity with which marked changes of functional activity take place. Frequent repetition of such tests is necessary if much information is to be obtained from them. An absence of phtalein for several days and a high blood urea concentration are grave findings.

**TREATMENT.**—The first object in the treatment is to relieve the congestion and inflammation, since the renal function is diminished by these conditions; by these means we restore the excretory function. It is, therefore, in order to restore the functional equilibrium by their antiphlogistic influence, that the single or combined use of diaphoretics and cathartics is availed of, and not with the thought that the skin and bowels should be made to perform the work normally done by the kidneys.

**Absolute rest in a warm bed** and in a warm room is of primary importance, and, in order to promote a constant and free action of the sweat-glands, **woolen underwear** and **blankets** should be used. These measures are of importance both in mild and severe cases.

The **diet** should consist of bland foods only. Proteins should be limited. Von Noorden gives thin gruels, fruit juices and sugars, withholding milk for a week or two, until the more acute symptoms have subsided. **Salt** should be **interdicted**, and water or fluids allowed only in moderation, as they in-

crease the work of the kidneys, especially if edema is present. The diet may be gradually increased by the addition of milk—1 quart in 24 hours,—junket, custard, vegetable purées, crackers, cocoa, etc. Water can be given in increasing quantities when the urine is being freely passed.

**Milk** contains just enough salt to answer the demands of the tissues without harming the diseased organ. The **Karell course** of dieting serves the purpose, restricting the patient to 800 c.c. (1½ pints) of milk, given at 4-hour intervals during the day for a week. Thirst is allayed by moistening the lips, and hunger by chewing a little toast. After a week of this, 1 egg is allowed, without salt, and other fluids may be substituted as the ordinary diet is gradually resumed, but the total of 800 c.c. (1½ pints) must not be exceeded. The food should always be salt-poor but may include meat, fresh water fish, unsalted butter, cheese, eggs, rice, unsalted bread, potatoes, peas, beans, fruit, tea, coffee, chocolate, etc. With the diet thus regulated the heart and kidneys are spared to the utmost. Eustachio (Rif. Med., July 14, 1917).

The writer advises **rest in bed**, with the diet limited to **milk** and **cream** in equal parts for 4 or 5 days. Less albumin is excreted on this than if cereals are also given. He then adds **butter**, **potatoes**, and **rice**, all **unsalted**; some days later, **bread** and **cereals**; next, **cooked fruits** and other vegetables, and finally **eggs**. Such a progressive diet increase exerts a useful psychologic effect. Salt and protein restriction are of value even if there is no edema and urea excretion is normal. In some cases urenic headache subsided after **lumbar puncture**. Petré (Ann. de méd., June, 1921).

**Rest in bed**, whereby tissue breakdown is minimized and the activity of the skin maintained in eliminating fluid; a **diet** devoid of purin bodies and largely made up of starch, and in some cases the application of **dry cups** over

the kidneys, may be resorted to with the assurance that they can do no harm and very probably will do considerable good. Editorial (Therap. Gaz., June, 1923).

In regard to the **fluid intake** in the nephritis of childhood, it is best, as a rule, not to insist on restriction. It is generally safe to give as much water as the kidneys can take care of. In acute hemorrhagic nephritis harm would be done by not giving fluid in large amounts. An output of urine approximating  $\frac{2}{3}$  of the water intake is satisfactory. As much as 48 ounces of fluid can be taken by most nephritic children without a resulting gain in weight or edema. In pronounced edema, restriction may be advantageous, but 10 or 12 ounces should be considered the minimum. Diuretics are of doubtful utility, with the exception of **theobromine sodio-salicylate** in the nephrosis type of case. **Purging** and **sweating** are useful if not pushed to excess. In all cases with edema the **diet** should be **salt-free**. F. W. Schlutz (Minn. Med., Dec., 1924).

The milk diet generally prescribed in nephritis is unsuitable and possibly harmful, the quantity of milk required to maintain nutritive balance supplying an excess of fluid as well as of salt and protein.

In the cases of acute nephritis with reduced urinary output and uremic symptoms, the **diet** should consist of carbohydrates and fats, such as sugar, sweet fruits and fruit juices, flour, rice and washed butter with little salt. When the uremic symptoms recede, the yolks of 1 or 2 eggs may be allowed, and later, vegetables cooked with little salt and some milk. Still later, boiled meat, 50 to 100 Gm. a day, is permissible. Where the condition is wholly or chiefly one of *nephrosis*—featured by marked albuminuria and retention of water and salt, with milky blood serum and doubly refracting droplets in the urine,—stress is to be laid on a diet low in salt (only 2 Gm. a day) as well as in fluid. V. Kollert (Wien. klin. Woch., Jan. 8, 1925).

Particularly if any edema be present should a **salt-free diet** be the rule, as it has been shown that normal saline injections increase the amount of edema.

In the light of the occasionally brilliant results that have been obtained, and in view of the apparently simple (and correspondingly incomplete and inaccurate) explanations that have been offered, enthusiasm appears to have gone somewhat beyond bounds in regard to **salt restriction** as a therapeutic measure.

It is by no means a panacea for all nephritic edemas. With careful selection of types and with methodic regulation and control, salt restriction can probably never do harm and will usually do good; but employed as a routine measure without control, promiscuously, in every case of edema, it will more often disappoint than fulfill the expectations based on it. A. C. Croftan (Jour. Amer. Med. Assoc., Feb. 17, 1912).

The treatment employed by the author in war nephritis is stated by him to have given very satisfactory results. At first all patients were kept in **bed** until albumin and casts had disappeared from the urine and there was a fair salt and nitrogen balance, or until there seemed to be no prospect of the albumin and casts disappearing. The **diet** was limited to milk in the very severe cases and in the others it was fixed at  $2\frac{1}{2}$  pints ( $1\frac{1}{4}$  liters) of milk, 6 ounces (180 Gm.) of bread, 1 ounce (30 Gm.) of rice, 4 ounces (120 Gm.) each, of potatoes and greens,  $\frac{1}{2}$  ounce (15 Gm.) of butter and 1 ounce (30 Gm.) of jam, with fruit occasionally. The food was prepared without addition of salt, except in the green vegetables. As improvement progressed, bread was increased, egg yolk added, and later small amounts of fish or chicken permitted. The diet was always given by weight. **Water** was allowed **freely**. Simple **diaphoretics**, saline or other **purgatives**, and **hot air baths** were used when necessary.

**Nitroglycerin** was given when the blood-pressure was high. **Iron** followed in the later stages for anemia. Where there was deficient secretion of urine, **Fischer's sodium carbonate treatment** was employed, beginning with hourly doses of 0.6 to 1 Gm. (10 to 15 grains) of pure crystalline sodium carbonate in 250 c.c. ( $\frac{1}{2}$  pint) of water and increasing the interval between doses when there was free diuresis. **Digitalis** and **caffeine** were also employed, alone, together, or combined with the alkaline treatment when it failed to promote an adequate diuresis. Sensations of great prostration were much relieved by the administration every 4 hours of **epinephrin** in doses of 0.2 to 0.3 c.c. ( $3\frac{1}{2}$  to 5 grains). J. M. Clarke (Brit. Med. Jour., Aug. 25, 1917).

In nephritis one should avoid, remove, and combat every condition that favors the abnormal production or accumulation of acids and substances acting like acids in the kidney. In threatened or established cases, one should give **alkali, salts, and water**. The alkali neutralizes the acid present in abnormal amount in the kidney, the salts are indicated because the various changes induced in the kidney colloids by acid are counteracted by adding to such acid any salt, even a neutral salt, and the water is given in order to have more of it present than is necessary to saturate all the body colloids, as otherwise there is no free water left for the secretion of urine. Active administration of **sugar** either by rectum or intravenously is advantageous; carbohydrate starvation is a common cause of acidosis and sugar is very efficient in reducing hydration. Martin Fischer (Penna. Med. Jour., Jan., 1918).

In rare cases in which there is severe pain, local **bloodletting**, by means of leeches or cupping over the loins, may be useful; these measures are seldom needed, however, and a more salutary effect may often be gained by **hot fomentations**.

Bacelli's method of treatment of the early stage of acute nephritis consists of the abstraction of blood from the foot. The treatment is based on the fact that the venous pressure in the kidney is high, and that when the organ is inflamed the pressure is still greater. This leads to degeneration of the renal epithelium. **Bleeding from the foot** tends to cause a diminution of pressure in the inferior vena cava, and hence also in the renal veins. The amount of blood to be withdrawn according to De Rossi, varies in the individual case, but in the adult should not be less than 300 c.c.; in children the amount should be proportionately smaller.

Copious **venesection** followed by **transfusion** of normal blood inhibits the characteristic degeneration usually found in the epithelium of the ascending loop of Henle in the kidneys of dogs acutely poisoned by mercuric chloride. Burmeister (Jour. Labor. and Clin. Med., Apr., 1917).

In tubular nephritis in children, often due to nasal sinus infection, the most striking benefit is seen when the causative sinusitis can be cured. This can occasionally be accomplished by means of **irrigations of the nares** with alkaline salt solutions, *e.g.*, **sodium chloride** and **bicarbonate**, of each 0.75 per cent. Instillations of **mercurochrome** in 1 per cent. solution seemed to benefit one patient. The diet should not be limited in these cases. Clausen (Atlantic Med. Jour., Jan., 1926).

Diminution of the edema and the elimination of urea and other urinary constituents retained in acute nephritis are best attained by exciting a profuse perspiration. The congestion of the kidneys is also relieved by this vicarious action of the skin. The same results may also be accomplished by means of the **hot-air or hot-water bath** and the **hot, wet pack**; in most cases the last method proves effective. It is easily applied by wringing a blanket out of hot water, wrapping the patient in it, and surrounding him, first, with a dry blanket and, finally, with a

rubber cloth. According to the condition, the patient may remain in this improvised steam bath until free sweating has continued for an hour or more. Children suffering from scarlatinal nephritis may either be treated thus, or by immersion in hot water for twenty, thirty, or more minutes; the child is then wrapped in warm sheets or blankets, after lightly drying the skin, and warmly covered in bed.

Strasser and Blumenkranz found the effect of **warm baths** of considerable duration decidedly beneficial, the excretion of nitrogenous bodies and sodium chloride being greatly augmented, while the total volume of the urine also was considerably increased. They suggest 1 or 2 baths daily of from 1 to 1½ hours' duration in suitable cases.

For the application of **dry heat** in children affected with nephritis the writer has employed the following simple method: The child rests in bed with an ice-bag on its head. The bedclothes are pinned tightly around its neck and lower down kept elevated by wooden arches, forming a species of tent. At the foot of the bed the heat generated by a lamp in a box is admitted through a tin pipe. The duration of the treatment is between ½ and 1½ hours, the temperature reaching a maximum of 55° C. These treatments are always well borne, with no unpleasant effects. G. B. Allaria (La Ped., June, 1911).

In the presence of nausea in nephritis the writer makes no attempt to give the patient any food whatever, although water is given by rectum in **normal salt solution**—8 ounces every 4 hours by the drop method. If much edema is present, purgation by **magnesium sulphate** and **hot air baths** are employed, but these measures are never prescribed in the absence of edema as they may then be dangerous or even fatal. The hot air bath is, next to bleeding, the best method of reducing high blood-pressure. When nausea ceases, the **diet** is ordered, ex-

cluding proteins, especially meats and salt. The diet at this stage consists mainly of milk. Later carbohydrates are added, along with fats, but the proteins are kept low. R. C. Cabot (L. I. Med. Jour., Aug., 1917).

In studying the dehydrating action of calcium and magnesium salts in acute nephritis the writers observed a lowering of the blood-pressure following intravenous injection of a 2 per cent. solution of **magnesium sulphate**. In the selected cases in which this measure was used, the blood-pressure promptly fell and remained at a low level for about 5 hours. With the fall in pressure, headache, visual disturbances and convulsions were abated, and the injection was usually followed by diuresis, diaphoresis or free catharsis. The fall in blood-pressure usually began after the introduction of 15 to 20 c.c. (½ to ⅔ ounce) of the solution. When the introduction was conducted slowly, at the rate of 10 c.c. per minute, no change in the respiratory or cardiac rates occurred. The total amount given at a single injection never exceeded 10 c.c. per kilo. of body weight. There was no apparent effect on the albuminuria or hematuria. Blackfan and Mills (Arch. of Ped., July, 1923).

In cases in which a sudden onset or acute suppression occurs, prompt relief often follows **high rectal irrigation** by a gallon of plain water or normal saline at from 100° to 110° F., repeated every four hours until the function is again established. **Hot air** or **vapor** may also be generated beside the bed and introduced beneath the cradled bedclothing by means of a tin funnel and pipe. The drinking of **hot lemonade** or **soda-water**, or of **water containing spirit of Mindererus**, will stimulate the sweating. Should these measures fail, as in uremia, perspiration may be started by an hypodermic injection of **pilocarpine**, ⅛ to ¼ grain (0.008 to 0.01 Gm.); it will then

continue to pour out upon the application of heat. Serious consequences sometimes attend the use of pilocarpine, and the heart and pulse must always be carefully watched. A safe rule is not to use this drug if any edema of the lungs be present. The sweating should be repeated as often as the patient's strength will permit, until the dropsy disappears.

Hydragogues, as **elaterium**, the **saline cathartics**, and **compound jalap powder**, are useful as adjuvant measures. The extract of elaterium ( $\frac{1}{8}$  to  $\frac{1}{4}$  grain—0.01 to 0.016 Gm.) is prompt in action, and **magnesium or sodium sulphate** (1 dram—4 Gm.) given in hot concentrated solution every hour, or a **calomel** purge, may also be recommended. In extreme cases of dropsy it may be necessary to relieve the tension and distress by the use of a small **trocar** and **cannula**, with a **drainage-tube** (Southey) attached to the latter after the trocar is withdrawn, or by multiple punctures. If either hydrothorax, hydropericardium, or ascites assumes serious features, **aspirations** will become necessary. To the diaphoretic treatment may be added  $\frac{1}{2}$ -ounce (0.032 Gm.) doses of the **spirit of Mindererus in water**. This, combined with **aconite**, aids in controlling the fever that may be present and in preventing the vasoconstriction that is often premonitory of uremic symptoms.

The writer tried Wright's **vaccine** technique in colon-bacillus nephritis and pyelitis. Though he undertook it with much skepticism, he has become convinced of its great value. In 4 of the 12 patients thus treated there was prompt recovery after failure of all other measures. It should always be tried in all cases rebellious

to other methods. The reaction, both general and local, was surprisingly mild. Rovsing (Hospitalstidende, May 12, 1909).

In the treatment of infectious nephritis the specific drug indicated should be used without much regard for its action on the kidney. In syphilitics it is hard to know whether the nephritis is of syphilitic nature or not, but in the presence of a negative Wassermann finding mercury should be avoided. **Diphtheria antitoxin** is useful in the nephritis that accompanies diphtheria. In streptococcus or staphylococcus nephritis, **vaccines** should be used according to Wright's technique; this may also prove useful in nephritis from the diplococcus, etc. In acute nephritis with fever, drugs to reduce the fever should be avoided. The febrile process is treated by graduated **hydrotherapy**. Arcangeli (Policlinico, Med. Section, April, 1910).

In the nephritis of childhood the writer advises as follows: 1. For two days prohibit all food, giving only 500 or 600 Gm. (1 pint or 20 ounces) of water, sweetened with table- or milk- sugar, daily. Then give 500 Gm. of milk and same amount of water. When condition becomes sub-acute, add carbohydrates, as preparations of flour, potatoes, etc. Add sugar to milk; when distasteful, dilute milk with Vichy, or give it alternately raw and boiled. Where **milk diet** not tolerated or results poor, try salt-free diet, omitting proteids and limiting milk to small amounts. Later, if no complications, lean ham, fresh pork, lamb, and chicken may be given. Milk should not be taken with meals. 2. **Rest in bed** and avoidance of exposure. 3. Stimulate skin by **general rubbings**, gentle **massage**, and **tepid baths**. **Hot pack**. 4. **Dry cupping**, **wet cupping**, or **leeching** over triangle of Petit. 5. **Systematic disinfection** of mouth, nasal fossæ, and pharynx, and treatment of skin lesions as possible portals of infection. Where excretory insufficiency appears: 6. **Hot-air** or **vapor baths**. 7.

**Drastic purgative, followed by laxative.** When signs of intoxication appear: 8. **Theobromine**, 0.5 Gm., at most 0.75 Gm. ( $7\frac{1}{2}$  or  $11\frac{1}{2}$  grains) at a dose in child of 10 to 13 years. **Powdered squill**, **digitalis**, and **scammony**, 0.025 Gm. ( $\frac{1}{4}$  grain) of each in a pill, given two or three times daily. If circulation weakens, **digitalin** or **infusion of digitalis**. **Convallaria** or **convallamarin**. Hutinel (Bull. méd., Feb. 16, 1910).

In 2 cases of acute and 1 of chronic nephritis remarkable benefit was obtained with **adrenalin**. To a child nearly 5, the writer gave 16 drops a day of the 1:1000 solution, 4 drops at 4-hour intervals. The adults were given 40 drops a day, 8 at a time. Borelli (Polielinico, Apr. 30, 1916).

Mercury does not seem advisable in treatment of the nephritis with inherited syphilis. The writer has even witnessed hematuria follow mercuric inunctions, and consequently he refrains from mercury in treatment of nephritis with suspected inherited syphilis. Intravenous injection of an **arsphenamin** preparation is now his procedure. The diuresis increases and the general condition improves, but we must not expect rapid improvement or a definite cure. These can be counted on only when treatment is begun in the early stage. Hutinel (Paris méd., Jan. 25, 1919).

Two cases of acute nephritis, unaccountable otherwise than through their coexistence with syphilis, in which **antisyphilitic treatment**, in particular **neoarsphenamin**, was followed by good results. D. N. Silverman (N. O. Med. and Surg. Jour., Apr., 1921).

In toxic acute nephritis such as may follow tonsillitis, the author approves of a **hot pack**, either general or limited to the middle zone of the body, on alternate days. In parenchymatous nephritis, he would **limit water intake** to amounts compensative for loss through the lungs, skin, and kidneys. **Hot packs** and **sweet spirit of niter** in moderate doses are indicated. After a number of days a **diuretic** may be tried for a day or two; if it succeeds,

an interval of 2 days should elapse before the next diuresis. **Nitroglycerin**,  $\frac{1}{100}$  grain (0.0006 Gm.), often seems to act as diuretic. Hare (Therap. Gaz., Sept., 1921).

In 12 cases of acute nephritis in children, absolute **rest in bed** was ordered until the urine had been albumin-free at least 4 days. For the 1st week a rigid **milk diet** was used, followed by gradual addition of eggs, cereals and fish. **Salt** was **excluded** throughout, and the **protein reduced**. A mixture containing **tincture of hyoscyamus**, 5 minims (0.3 c.c.), and **potassium citrate**, 5 grains (0.3 Gm.), was given 3 times a day during the acute stage, and later, **iron** in the form of the **saccharated carbonate** spread on bread and butter. Removal of the focus of infection, *viz.*, **tonsillectomy** and **adenoidectomy**, was carried out at the conclusion of the acute stage, unless the urine failed to become albumin-free and relapses occurred, in which case the operation was performed without delay. All the cases recovered. R. S. Allison (Pract., Mar., 1925).

In acute nephritis, aside from **purgation**, a **hunger and thirst** treatment for 3 to 5 or more days is necessary for the prevention of cardiac dilatation and eclamptic pseudo-uremia. Such treatment also obviates chronic nephritis. All cases of acute nephritis should be regarded as having a serious affection of the heart; **digitalis** should nearly always be given until the pulse rate is down to 50 or 60. Where there is renal insufficiency a **diet** poor in proteins and salt should be ordered, and in grave cases, a vegetable diet. In anuria that has lasted 2 or 3 days, such procedures as **renal decapsulation**, **X-ray** exposure of the kidney, or **anesthesia of the splanchnic nerve** become necessary. For a simple hematuria, no dieting is required, but merely the **removal of the focus of infection**, *e.g.*, the tonsils or teeth. A **dry, salt-free diet** overcomes edema where there are no evidences of renal insufficiency. Sometimes large doses of **urea**, or **thyroid gland**, are required. F. Volhard (Zeit. f. Urol., xix, 5, 1925).

If the uremic convulsions do not promptly yield to diaphoresis and catharsis, **venesection** must be resorted to, the withdrawal of as much as a pint or two of blood often saving life. Occasionally **inhalations of chloroform** are needed to subdue the violent convulsive seizures, as in eclampsia. Their recurrence may be prevented by the use of **rectal injections of potassium bromide** (1 dram—4 Gm.) and **chloral hydrate** ( $\frac{1}{2}$  dram—2 Gm.).

Contraction of the arteries with increased tension and beginning muscular twitchings requires the use of **chloral hydrate**, **nitroglycerin**, and, possibly, **morphine**.

Nausea and vomiting may be held in control by minute doses of **cocaine**, **cracked ice**, **dilute hydrocyanic** or **hydrochloric acid**, **bismuth**, or by the addition of **soda-** or **lime-water** to the milk.

There is little advantage in diuretics other than the simple diluent drinks already mentioned, at least early in the course of the disease. Later, **potassium bitartrate** or **acetate**, **sodium benzoate**, as adjuvants to the water, and **stimulants** to relieve cardiac depression, or **caffeine citrate** and the **infusion of digitalis**, may be given, well diluted.

The writer recommends **serum** of blood drawn from the **renal vein** of the goat after trying it in 4 cases in which this serotherapy was systematically applied. The results encourage its further use in acute exacerbations of chronic nephritis, in all infectious diseases with threatening uremia, in cases of excessive arterial tension supposedly of renal origin, and whenever uremia is installed, regardless of its origin. The writer administered without by-effects from 10 to 110 c.c. (162 minims to  $3\frac{1}{2}$  ounces) as the daily dose, but for fear of accidents

from serum sickness never gave over 20, 30, or 40 c.c. ( $\frac{3}{4}$ , 1,  $1\frac{1}{2}$  ounces) at a time. In the first case the interstitial nephritis was in the terminal stage, but under the serotherapy 1500 c.c. (50 ounces) of urine were voided and 3 per thousand chlorides, the headache and dyspnea subsided, and the blood-pressure dropped,—effects which months of other treatment and dieting had not been able to procure. M. T. M. Bisso (*Semana Medica*, Buenos Aires, Feb. 15, 1912).

**Renal organotherapy** was applied by the writer in a case of a robust young man who, in the second or third week of an attack of influenza, suddenly developed pulmonary edema. The right kidney and ureter were found to be extremely tender, and the left slightly so. The symptoms of acute nephritis becoming more threatening, with a tendency to coma, the patient was given a subcutaneous injection of 10 c.c. of **serum from the renal vein of a goat**. Seventeen hours later copious diuresis set in and the alarming symptoms subsided. The injection was repeated the next day, and organotherapy thereafter continued with **kidney extract**. This being suspended after 3 days, next day there was another, but less severe, attack of pulmonary edema. Recovery occurred. The dyspnea was ascribed to toxic weakness of the heart, and **citrate caffeine** given by the mouth or subcutaneously was promptly effectual. Gil y Ortega (*Siglo Medico*, Sept. 8, 1917).

Care must be taken during convalescence that the patient be not exposed to cold. The diet must not be changed to solids either too suddenly or too rapidly, and particularly does this rule hold in the matter of meats. Milk should form the mainstay of the dietary, and light, watery vegetables, fruits, and cereals may be gradually added. The anemia will indicate the ferruginous tonics.

Carefully regulated habits in regard to dress, exercise, and diet, and a change to a warmer, drier, and more

equable climate, are necessary in cases that are convalescent from the very serious forms of nephritis, in which the renal parenchyma, by the persistence, at intervals, of a slight albuminuria, is shown to have been somewhat damaged.

Surgical procedures such as **renal decapsulation** and **nephrotomy** have been recommended by some observers.

A boy aged 12 had an ordinary case of scarlet fever, but twenty days after the onset of the fever he was taken with very severe vomiting; twelve hours later he had a hard convulsion, and passed a small amount of bloody urine heavily loaded with albumin. The boy was put in hot packs with hot linseed poultices over the kidneys, and pilocarpine and digitalin given hypodermically. This treatment was followed four successive days with no apparent benefit. On the morning of the fifth day there was complete loss of vision and hearing, and a few hours later the patient lapsed into unconsciousness, with complete suppression of urine.

Under ether anesthesia both kidneys were **decapsulated** at the same time. They were found to be as large as an adult's kidneys, very tense and congested. On removal of the capsule the blood fairly boiled from the kidney surface, showing the very high pressure it was under.

The first twenty-four hours after operation the apparently functionless kidneys secreted 24 ounces of urine. On the third day sight and hearing began to return, and at the end of the first week both were normal. The kidneys were also secreting the normal amount of urine. G. F. Harding (Jour. Amer. Med. Assoc., July 10, 1909).

In addition to parenchymatous and interstitial forms of nephritis, the author recognizes a *hematogenous form*, i.e., an infection with living micro-organisms. In the fulminating forms, if both kidneys are involved, as with streptococcus, death results; if unilateral, early **nephrectomy** may save life. In subacute

cases, septic infarcts and cortical abscesses may necessitate nephrectomy, or spontaneous evacuation of a cortical abscess in the fatty tissues may lead to a perinephritic abscess, or a pyonephrosis may occur. As the pus-producing cocci in these cases is of relatively short life, no living micro-organisms may be found in the later stages. The kidney may frequently recover its function, and if painful scars remain, the pain may be relieved by **capsulotomy**. W. J. Mayo (Jour. Amer. Med. Assoc., Oct. 4, 1919).

**Nephrotomy**, i.e., incision of the renal parenchyma, is preferred by the writer to either nephrectomy or decapsulation. Of 5 cases of acute nephritis subjected to nephrotomy after failure of all medical measures, all recovered. Of 2 nephrectomized cases, 1 recovered; the other, he believes, might have recovered if nephrotomy had been done instead. Whereas decapsulation merely remedies the congestion, nephrotomy permits, in addition, **antisepsis** and **drainage**, which is all that is necessary to cure the case. Pousson (Jour. d'urol., May-June, 1921).

Case of suppurative nephritis in a boy about 5 years of age who had had an appendectomy 6 weeks before. Cystoscopy showed indigocarmine excreted from the left ureter in 4 minutes, while none appeared from the right, which exuded pus profusely. Complete recovery followed **nephrectomy**. E. L. Bauer (Arch. of Ped., May, 1922).

From **renal decapsulation** improvement has been noted in approximately 65 per cent. of the published cases, and the mortality has been 5 to 10 per cent. The best results have been reported in acute nephritis and anuria; next, in chronic nephritis with edema. When there is no edema not much can be expected from the operation. The kidney may be decapsulated in any case that has a poor prognosis—when other means have failed and a fatal outcome is expected shortly. Except in acute nephritis the ultimate prognosis is necessarily bad, but there



seems evidence that life has been prolonged by the operation for months or even years. Bessesen (Amer. Jour. of Surg., Nov., 1924).

The writer deems **renal decapsulation** advisable only in uremia with oliguria, especially if there is renal pain—nephritis hemorrhagica dolorosa. He has seldom had success with it in subacute or chronic nephritis or in the nephrosis of bichloride poisoning. H. Strauss (Zeit. f. Urol., xix, 481, 1925).

**CHRONIC EXUDATIVE NEPHRITIS**, or **CHRONIC PARENCHYMATOUS NEPHRITIS**, sometimes termed **Chronic Bright's Disease**; **Chronic Diffuse Nephritis with Exudation**; **Chronic Tubal and Chronic Desquamative Nephritis**; **Large White Kidney**; **Secondary or Fatty and Contracted Kidney**.

**DEFINITION.**—A chronic diffuse inflammation of the kidneys, attended with epithelial degeneration, exudation from the blood-vessels, and permanent connective-tissue changes in the renal stroma. This is one of the two classic varieties of chronic Bright's disease, and is identical with Delafield's chronic productive (or diffuse) nephritis with exudation.

Two groups of cases corresponding to the clinical syndrome of chronic parenchymatous nephritis have been recognized by Volhard on the basis of differences in the blood-pressure. In the cases without increase of blood-pressure (*focal nephritis*) there is found *post mortem* the so-called "large white kidney"; microscopically, degeneration of the epithelium of the tubules is found, but inflammatory changes such as hyperemia and proliferation are wanting. In the cases with increase of blood-pressure (*diffuse glomerulonephritis*), inflammatory changes in the glomeruli are observed. These cases are further subdivided into those with and without edema, the former condition existing where epithelial degeneration is pronounced and diffuse. Subsequently, according to Fahr, a secondary inflammatory process

may supervene in the interstitial tissue, contraction of the kidney thus resulting.

In one of the two great groups of the subacute and chronic affections of the kidney, the predominating, or even the only apparent, symptom is edema. Its intensity and general distribution at once point to the condition as a *hydremic nephritis* (chronic parenchymatous nephritis). The urine always contains much protein; if not, the edema generally has its source in some organ other than the kidney. In pure hydremic nephritis the only difficulty on the part of the kidney seems to be the excretion of salt and water; waste products are eliminated as usual. The condition frequently progresses, however, toward a phase characterized by retention of wastes as well as edema; at this stage, the condition is practically the same as that found in chronic interstitial nephritis. A case beginning with typical hydremic nephritis may in a few months show all the symptoms (retention of nitrogenous wastes, urine of low specific gravity, cardiovascular and eye changes, etc.) of the chronic interstitial disease. Hydremic nephritis is easily diagnosed on the basis of extreme edema and ascites, very large amounts of protein, and abundant granular and hyaline casts. Prognosis, however, is extremely difficult. While many cases recover, a larger number progress more or less rapidly to death by uremia. H. MacLean (Lancet, June 6, 1925).

**SYMPTOMS.**—The symptoms of an acute parenchymatous nephritis may persist in a lesser degree until the condition becomes a chronic one; particularly is this true of the albuminuria, the anemia, and the dropsy. As a rule, however, the disease develops slowly and gradually, and in a subacute manner, although there is seldom an early indication of renal derangement. There may be merely a loss of appetite, attacks of indigestion, nausea, headache, dullness, perhaps some pallor, and a general impairment of health and strength.

The complexion then takes on a blanched appearance, and there is soon puffiness of the eyelids, or swelling of the feet or ankles, or both. There is a gradual extension of the edema up the legs, and as the day grows it becomes worse; on rising in the morning it may have entirely disappeared. In the majority of cases the quantity of urine is diminished. In the later stages of the disease, however, it may be nearly or quite normal, and in protracted cases of pale contracted kidney, or when absorption of the dropsical effusion is in progress, it may even be slightly increased.

An acute nephritis supervening upon the chronic condition may now cause a very scanty or suppressed secretion of urine.

In cases of scanty urine the specific gravity is, of course, increased, and *vice versâ*.

Albuminuria is often present to a decided degree. The albumin may constitute as much as from one-fourth to three-fourths of the urine in volume, or from 1 to 3 per cent. by weight.

In an attempt to ascertain to what extent protein lost as albumin in the urine can be replaced by food protein the writers made a study of the nitrogen metabolism of cases of acute and chronic parenchymatous nephritis. The total urinary nitrogen did not prove a satisfactory measure of nitrogen katabolism, which could be estimated only from the urinary non-protein nitrogen, after proper allowances for changes in blood and tissue non-protein nitrogen and variations of body weight due to diuresis or accumulation of edema. By giving large amounts of carbohydrate and fat it proved possible to reduce the protein katabolism to 0.5 to 0.7 Gm. per kilo. a day. If enough protein was given to cover the nitrogen katabolism plus an additional

amount equivalent to that lost as albumin in the urine, nitrogen wastage could be prevented. J. P. Peters and H. A. Bulger (Arch. of Int. Med., Feb., 1926).

The nitrogen coefficient, *i.e.*, the relation of the urea to the total nitrogen, is reduced from the normal (80 to 82) to 60. The urine contains an abundant sediment, consisting of urates, casts, red and white blood-corpuscles, epithelial cells, granular *débris*, and fatty granular cells, and is in color turbid and sometimes smoky yellow. There are tube-casts of different varieties, the narrow or broad hyaline, fatty granular, and epithelial casts being most commonly noted.

Casts may be absent from a certain number of cases which otherwise are typical cases of nephritis, being destroyed by lysis resulting from the action of the *Bacillus coli*.

Again, albuminuria is by no means always indicative of permanent disease, unless considerable in amount and more or less constant in occurrence.

The nature of the accompanying tube-casts must not be too greatly relied on to determine the seriousness of the renal lesion. Even the definite hyaline cast, as distinguished from the insignificant cylindroids of the mildest grades of renal irritation, is so frequent in arteriosclerosis, cardiac or hepatic disease, and in gouty conditions, that its significance is comparatively trivial without general corroborative clinical symptoms.

According to Schütgen, the leucocytes occurring in the urine in Bright's disease are lymphocytes.

In certain cases, according to this author, the presence of lymphocytes alone in the sediment is capable of affording a differentiation between Bright's disease and renal abscess or pyelonephritis.

The author approves of Mallory's division of nephritis into the tubular, glomerular, and vascular types. (1) Tubular nephritis is rarely seen. It is almost always acute and due to a poison, especially corrosive subli-

mate. (2) In acute glomerular nephritis all parts of the kidneys are affected but the glomeruli far more than the tubules and vessels. The condition is usually part of a general streptococcus infection and is to be feared in every severe case of tonsillitis. (3) Vascular nephritis is the ordinary nephritis of old people, *i.e.*, arteriosclerosis, producing a scarred and broken-down kidney. There is always general arteriosclerosis as well, but the renal involvement may be altogether out of proportion to the involvement of the arteries elsewhere. Chronic interstitial nephritis is the end result of all types of nephritis provided they last long enough, and is not a special variety, and does not cause a peculiar clinical type identifiable by the urinary findings or in any other way. In well-marked nephritis with a low blood-pressure, amyloid degeneration may be suspected.

Of the albuminurias which are not nephritis, the only one of importance is the so-called "albuminuria of adolescence," sometimes called cyclic or orthostatic albuminuria. Lee examining freshmen entering Harvard, found that about 10 per cent. had a well-marked albuminuria, only rarely with a genuine nephritis. The severe case of tubular nephritis depends for a diagnosis mostly on a knowledge of the cause. The urine is not characteristic in itself. It is impossible to distinguish the urine of mild tubular nephritis from the urine of passive congestion of the kidney, of anemic states or febrile states, or of many other conditions in which one finds albumin and casts in small quantities.

Acute glomerular nephritis, in the author's experience, with post-mortem work, proved to be one of the most difficult of diagnosis to make. Only in a small minority of cases are there characteristic manifestations, *viz.*, (a) uremic symptoms, such as headache, vomiting, convulsions, coma; (b) general edema; (c) high blood-pressure, and (d) the urine in which the most characteristic thing is

the presence of blood. There may be considerable diminution in the amount of urine, but not such extreme diminutions as in toxic tubular nephritis. Cases diagnosed as acute glomerular nephritis were generally found to be chronic at autopsy.

In the subacute or chronic cases there is blood in the sediment, but as they go on the blood diminishes and the fat increases. Later, the casts diminish until in the later years it may be impossible to find any at all. If one finds a large number of casts in the urine one can be fairly sure that the kidney is not badly damaged. Casts are of no value in the diagnosis of renal disease because they are found so often in diseases which are not nephritis, because they are so often lacking in nephritis, and also because we have now so many tests of the kidney function which are superior in value to the examination for casts.

One of the most valuable signs of chronic nephritis is the measurement of the day and night urine. The night amount may be twice the day amount, or even more. The author always instructs patients to collect separately the day urine, 7 A.M. to 7 P.M., and the night urine 7 P.M. to 7 A.M., to measure them, then to mix them and bring him a mixed specimen of the total amount. With the increased amount at night goes a progressive fall in the specific gravity. Another point is the fixation of the specific gravity, *viz.*, if one gives the patient abundant water one cannot dilute his urine and when water is withheld one cannot concentrate his urine. In making the test, one has him pass his urine, as far as possible, every 2 hours during the day time and as frequently as he conveniently can during the night. With this goes, in most cases, a retention of nitrogen, to be tested best by the Folin tests in the blood. The retained nitrogen in normal people is somewhere between 25 and 40 milligrams per 100 c.c., and in the nephritis cases it runs up to 100, 150 and

even 200. This retention is a threat of impending uremia.

A diagnosis of acute uremia is often wrong because the condition is apt to cause coma and the urine in any case of coma is practically certain to contain albumin and casts in considerable amount. One should never make a diagnosis of acute uremia without evidence in the heart, subcutaneous tissues (edema), and history.

Chronic vascular nephritis is a slow gradual process. The specific gravity of the urine is not so low, the nocturnal polyuria not so great, the specific gravity not so fixed, but in other respects it is almost impossible to distinguish it from chronic glomerular nephritis. Age is the chief differentiating point. Another point is that anenmia is not nearly so prone to develop in chronic vascular nephritis. The retinae have not served the author well as a means of differential diagnosis. Urea determinations depend primarily on the food. A much more accurate test of renal function than the urea output is the phthalein test.

If a nephritis is acute and if it is diagnosable at all, there are perfectly diagnosable signs in the urine. If chronic, it will show in the heart in practically every case and in the blood-pressure. R. C. Cabot (Med. Standard, Oct., 1917).

Absence of albuminuria must not be taken as definitely excluding chronic nephritis where the symptoms of arterial pressure favor such a diagnosis. Resort must then be had to other methods, such as Ambard's coefficient, and great care taken in observing the patient. Urine containing but a trace of albumin not infrequently proves misleading, the renal disease turning out to be more grave than one has been led to believe it. H. Baril (L'Union méd. du Can., Apr., 1918).

Discussing *diffuse glomerulonephritis*, the writer mentions with approval Volhard's theory of an angiospastic ischemia of the glomeruli as the initial

phase of the condition. At first the condition is merely a functional one, with contraction of the arterial vessels proximal to the glomeruli, ascribed to such factors as exposure to cold and allergy or anaphylaxis from various causes. If the bloodlessness of glomeruli continues long enough, however, the glomerular changes become progressive, and the disease passes either into the rapidly fatal "subacute" form or the more slowly progressing "subchronic" form. The clinical phenomena of the acute stage are hematuria, with albumin and casts, edema, increase in the blood-pressure, blood changes, and as a complication, uremia. The high blood-pressure is regarded as a reflex measure calculated to force a sufficient amount of blood through the contracted arteries to the glomeruli and thus enable the latter to filter out a normal amount of urine. During the early, angiospastic stage it may be possible to relax the contracted vessels by treatment. According to Volhard, this can be done in some cases in the early acute stage merely by giving a large quantity of **water**. Later, when the glomeruli are organically diseased, there is defective removal from the blood of water as well as of waste products. The water accumulates, producing an actual hydremia, which in turn leads to the anemic appearances of the blood, with equal reduction of red cell count and hemoglobin. Elwyn (Amer. Jour. Med. Sci., Mar., 1923).

The edema is prominent and persistent, gradually extending all over the body; thus, pitting may be obtained on pressure on the limbs, chest, abdomen, and back.

The loose subcutaneous tissues, as of the penis, scrotum, and eyelids, are especially distended. Only in chronic hemorrhagic nephritis may the edema be absent or very slight. Chronic exudative nephritis, especially with large white kidney, shows a pasty, pallid skin and anasarca as its most distinguishing characteristics. For several months the

dropsy may be of moderate degree and almost stationary; it then grows worse insidiously, in spite of all efforts at treatment, and death ensues in a month or two.

There may be present in serious cases dropsy of the serous sacs, with its accompanying distressing symptoms; edema of the larynx and lungs may then supervene, causing sudden death. Dyspnea may occur, both toxic and nervous, as well as mechanical or cardiac, in origin. On lying down, cardiac dyspnea, due to failure of the heart's action and seen in many instances, is aggravated, as a rule.

It may be provoked by vasoconstriction, and is, in such cases, a signal of uremia.

With these conditions may be associated catarrhal bronchitis, with cough and expectoration.

There is frequently a moderate degree of cardiac hypertrophy of the left ventricle; later there are dilatation and weakness of both ventricles. There is an accentuation of the aortic second sound and an increase of the pulse-tension.

Headache, vertigo, sleeplessness, nausea and vomiting, diarrhea, and stupor, coma, or delirium may all develop and form the symptoms of a uremic condition.

These symptoms, as a rule, precede a fatal termination. The convulsions that are common to chronic nephritis without exudation do not appear, however. In quite a large number of cases albuminuric neuroretinitis occurs, and is evidenced by dimness of vision and field-defects. In certain cases of marked edematous distention the skin of the legs becomes subject to a red eczematous eruption. The temperature is practically normal in the absence of

such complicating inflammations as pericarditis, endocarditis, pneumonitis, and ulcerative colitis, all of which are rare conditions.

According to Ullman, a clinical sign observed in disease of the kidney at an early stage is a regular vibratory closure of the eyelids. The vibration affects usually the upper lids, most frequently one lid; rarely it occurs in the lower lids. If it occurs at the external commissure, the entire eye will share in the movement. The duration of the attacks is thirty minutes and sometimes more. The attacks may often be repeated for a number of days and then cease.

While exophthalmos accompanies Graves's disease, paralysis agitans, retrobulbar growths, brain tumor, sinus thrombosis, or hydrocephalus, and prominent eyes occur in cases of myopia and tuberculosis, its presence should always lead, according to Gordinier, to a careful consideration, in the diagnosis, of chronic nephritis, particularly if it is unaccompanied by thyroid enlargement or marked tachycardia.

Neuroretinitis albuminurica is seen but seldom in acute, diffuse glomerulo-nephritis, and in about one-half the cases of malignant renal sclerosis and of chronic diffuse glomerulo-nephritis in the stage of insufficiency. It is, in fact, related to disease of the glomeruli. Its absence is of value in differentiating between benign and malignant sclerosis. When it is present the patient cannot live over 2 years. The amaurosis of eclampsia is a manifestation of eclamptic uremia, in which the eye grounds are normal save for occasional papillary edema. The prognosis is good, and improvement usually follows lumbar puncture. The so-called pseudoureemic ocular disturbances are seen only in renal sclerosis. They are usually very fugacious, and are probably dependent on arteriosclerosis and spasm of the cerebral arteries. Machwitz and Rosenberg (*Münch. med. Woch.*, Oct. 31, 1916).

Experience in late years has shown that the ordinary urinary findings in nephritis do not accurately reflect the functional capacity of the kidneys.

Large amounts of albumin, casts, and even blood may be present, yet the kidneys be excreting all waste products normally. Conversely, cases with serious retention may show only a trace of albumin and a few casts. Diagnosis of the actual renal condition must depend, then, upon the clinical symptoms and upon functional tests.

One of the easiest and most useful tests, according to G. M. Piersol (N. Y. Med. Jour., Jan. 4, 1922), is a study of the *specific gravity and variations in volume of urine*. After breakfast, at about 10 A.M., urine is voided and placed in a separate bottle; thereafter separate samples are collected every 2 hours until 10 P.M.; the urine voided after 10 P.M. is added to that voided at 8 A.M. the next day. Fixation of the specific gravity at too high or too low a level strongly suggests impaired renal function and calls for further investigation. The specific gravity of the various specimens should vary, and in at least 1 specimen, should be 1020 or over. Estimation of the *sodium chloride and nitrogen excretion in the urine* is valuable. If more than 5 Gm. of sodium chloride is present in the 24-hour urine, too much salt is being ingested. Five or 6 Gm. of nitrogen in the urine means a protein intake of 35 to 20 Gm. a day, and is the lowest daily excretion compatible with a diet sufficient to maintain strength. The *phenolsulphonephthalein test* is perhaps the best index of total renal function, but does not throw light on whether the tubules or the glomeruli are especially involved. Normally, 10 Gm. of *sodium chloride*, added to a standard daily intake, is completely eliminated in 24 hours. With normal kidneys, the concentration of chlorides in the urine is about 1.8 per cent.; diseased kidneys often show no more than 0.5 to 0.3 per cent. Cardiac edema and exudate formation must, however, be excluded. Chloride retention may occur without edema, and *vice versa*. Defective salt elimination is a useful early index of renal impairment, especially in tubular nephritis. The *non-protein nitrogen* is of more importance than the urinary nitrogen. It increases in proportion to the degree of renal insufficiency.

*Blood uric acid* in amounts of 3 mgm. to 100 c.c. of blood or over is regarded by some as the most delicate evidence of impaired kidney function, but it may be increased in other conditions, such as gout, and should be considered only with other evidences of nephritis. Increase of *creatinin* is a late evidence. The *blood chloride* is normally 5.6 to 6.1 Gm. to the liter; if poor salt-eliminating power exists, it may rise to 7.1 Gm.

The index of urea excretion derived from Ambard's laws by McLean gives much more information as to the degree of renal impairment and the prognosis than does the blood urea determination alone. Chronic nephritis with normal blood-pressure may or may not have sufficient renal impairment to alter the relation which normally exists between the blood urea concentration and the urea excretion, that is, it may have a normal or a low index of urea excretion. In general, the phenolsulphonephthalein test parallels the index of urea excretion; but there are marked exceptions to this rule in which the phenolsulphonephthalein test apparently gives an erroneous idea of the degree of renal impairment. R. L. I. Smith (Jour. Amer. Med. Assoc., Jan. 27, 1917).

A close parallelism exists among the new tests for determining renal insufficiency and early nephritis. For general applicability the author recommends first the determination of the fluid intake and output with special reference to the fixation of quantity and specific gravity and to nocturnal polyuria. If any irregularities appear from this procedure, they can then be supplemented by the more difficult tests. The phenolsulphonephthalein test is always necessary. These procedures can be applied by any physician. Of the more complicated blood tests, the estimation in order are the urea nitrogen and the non-protein nitrogen retention after proper consideration of the protein intake. The late appearance of *creatinin* would appear to give this test doubtful value as a diagnostic procedure, since by this time the other

tests are equally instructive and the subjective symptoms themselves hardly admit of an incorrect diagnosis. The point, however, as to its prognostic value is well taken. When all the foregoing tests have been applied, Ambard's constant is no additional labor. C. W. Dowden (Ky. Med. Jour., May 1, 1917).

Extrarenal factors such as severe anemia or cardiac decompensation influence renal function profoundly. Under such conditions renal function tests may indicate advanced nephritis and yet the kidney itself be structurally sound. If renal function is depressed, one must determine by thorough examination whether it comes from a pathological kidney or from extrarenal disturbance before drawing conclusions. Improvement of renal function accompanying improvement of extrarenal conditions is an indication of a structurally sound kidney.

If renal function is poor in the absence of serious disturbance in other organs, the probability of improvement in renal function is slight, except in acute nephritis. In chronic nephritis prognosis can be determined from renal function with greater success than in extensive extrarenal disturbances. Where progression of the disease seems to be by sudden exacerbations the prognosis must be more guarded than where progression is steady.

In hospital practice the author makes use of four tests: (1) Phenolsulphonephthalein elimination; (2) blood urea and rate of urea excretion; (3) specific gravity, sodium chloride and nitrogen content of the urine collected in 2-hour portions during the day, with special diet; (4) the amount of diuresis produced by such a diuretic as theophylline. When blood urea is not increased considerably, the kidney can be excluded as a cause of coma or other serious symptoms and prognosis depends on existing extrarenal disturbances. In mild cases the 2-hour test is particularly useful. The patient is put on a standardized diet for 2 days and on the third day the special meals

and the urinary collections are made. During the day, blood and urine are taken for the Ambard coefficient or the McLean index. If phthalein excretion is 35 to 45 per cent., moderate renal disturbance is present. If edema is marked and, in combination with digitalis, theophylline produces prompt diuresis, renal function is good; if not, it is poor and the prognosis worse. If phthalein elimination is below 35 per cent., renal function is poor and in patients without cardiac decompensation this indicates usually severe renal lesions. Ambard's coefficient usually parallels phthalein excretion. After phthalein excretion becomes low, determinations of blood urea are of value, for as they continue to rise they indicate a nearer approach to uremia. H. A. Christian (Penna. Med. Jour., xxi, 233, 1918).

Disturbances of the basal metabolic rate are sometimes met with in nephritis. High rates, up to + 50, have been ascribed to dyspnea and the restlessness often present in advanced cases. Acidosis is also a common accompaniment, and in the terminal stages of chronic glomerular nephritis pronounced reduction of the alkali reserve, frequently paralleling the condition of kidney function as revealed by functional tests, may exist.

The increased basal metabolic rate in chronic diffuse glomerular nephritis and in primary granular atrophy is not related to the amount of non-protein nitrogen; yet, where, as is sometimes feasible, the non-protein nitrogen is reduced to normal by a nitrogen-poor diet, the metabolic rate returns to normal, likewise. If the non-protein nitrogen is not reduced by such a diet, the metabolic rate also remains high, and the output of sulphates in the urine is likewise high. Nonnenbruch (Münch. med. Woch., June 26, 1925).

Chronic exudative nephritis may either continue from bad to worse, and

death may end all in a year or two; or anémia, albuminuria, and dropsy may appear in a person that has, for years previously, enjoyed apparently good health. After a first attack a second proves fatal within a few months. On the other hand, certain cases may show a slight pallor, a slightly diminished quantity of urine of high specific gravity and containing albumin, and yet may complain of no inconvenience for years. Decided attacks may then occur at intervals, during which the dropsy, dyspnea, etc., may be absent, although a certain amount of albuminuria persists; these attacks last for several months. The average duration of the disease varies from one and one-half to three years.

**ETIOLOGY.** — Chronic nephritis with exudation may either follow acute diffuse nephritis (as of scarlet fever or pregnancy), or simple chronic congestion and chronic degeneration of the kidneys. It arises insidiously more frequently, however, and without any previous acute manifestations. Males are more subject to this form of chronic Bright's disease than females. Cases occurring in children are usually preceded more or less recently by scarlatinal nephritis.

Young adults are more commonly affected with the usual form, developing subacutely. Drinkers of malt and alcoholic intoxicants seem especially liable to the disease. Even in cases where other manifestations are absent, it is not improbable that, in the insidious cases, some toxic or infectious agency may act slowly and persistently, and be the cause of the nephritis.

The disease has been observed in certain individuals living in malarial regions, and persons working under an exposure to cold and wet, or living in

humid, marshy districts, seem more liable to the renal malady than those who are more carefully shielded from such influences.

This so-called "parenchymatous" form of chronic Bright's disease may find its cause in tuberculosis, syphilis, or chronic suppuration, and in such cases it is usually combined with amyloid disease.

The rules of renal function in disease are not hard and fast. The classification of cases of chronic nephritis is imperfect. There are many atypical cases probably due to previous infections. The outlook in these cases is modified by the extent of fibrosis; when this is limited, life may not be shortened. Many of the arterial hypertension cases have endured for many years without appreciably deteriorating. Cases of cyanotic kidney due to cardiac disease, showing albumin and casts, clear up quickly when the heart improves. The prognosis in confirmed chronic parenchymatous nephritis is exceedingly grave, though not altogether hopeless. In the interstitial cases, the outlook is at times guardedly favorable if recognized early. J. M. Anders (*Med. Rec.*, Jan. 1, 1921).

Chronic nephritis is, generally speaking, caused by the combined effect of infection and abuse of protein. Among the Bedouins, whose usual diet is composed of a few dates and camel's milk, with rarely any meat, nephritis is practically unknown. Conversely, in the United States, there were in 1915, out of 909,155 deaths, 70,500 which were due to chronic nephritis. L. H. Newburgh (*Medicine*, Feb., 1923).

At the Öresund Hospital for Tuberculosis in 1917-1921 there were 3619 cases. Among these, 124 (3.4 per cent.) were complicated by albuminuria, nephritis and amyloid disease. Probably only a few of these represented genuine renal tuberculosis; in 45 it appeared that the renal disease was due to the tuberculosis. C. Holten (*Ugeskr. f. Læg.*, Sept. 18, 1924).



**PATHOLOGY.**—There are several types of kidney included in this disease, but the anatomic variations are dependent upon the cause and duration of the nephritis.

The *large white kidney* (without waxy degeneration) may be either normal in size or enlarged, and is pale or yellowish in color. The surface is smooth and the capsule is easily stripped off. On section the cortex appears broader than normally, and is either yellowish white throughout or may present opaque yellowish or whitish areas with mottling of red. In some cases the pyramids are congested. The following changes may commonly be observed microscopically: The renal epithelium is swollen, hyaline, granular, or fatty, and is more or less disintegrated or flattened; there is an enlargement of the glomeruli, owing to the growth of the capsule-cells and of the cells covering the capillaries, and, in certain cases, as a result of the connective-tissue thickening of the capsule, the tuft of capillaries is atrophied. There is some thickening of the arterial walls, and a moderate growth of connective tissue may be noted in patches around the glomeruli and tubules. The latter contain hyaline and granular casts.

The *small white kidney* (*secondary contracted kidney*) is, in most instances, probably a later stage of the preceding condition, in which the epithelial degeneration becomes more pronounced, and the connective-tissue growth and the resultant cicatricial contraction become prominent features. The kidneys are about normal in size, owing to a shrinkage in the large white kidney. The surface is slightly granular and the capsule proportionately adherent. In color they are usually grayish or yellowish (pale granular), and there may be a certain

amount of red mottling. The consistency is firmer than that of the large white kidney, and the surface, on section, shows, in the somewhat narrowed cortex, yellowish-white foci of fatty-degenerated epithelium; hence the term "small, granular, fatty kidney." Microscopically we find extensive degeneration and disintegration of the epithelium of the glomeruli and convoluted tubules, atrophy of the parenchyma, and a corresponding increase in the interstitial connective tissue. There may be an associated waxy degeneration.

The secondarily contracted kidney is characterized by a very diffuse fibrosis of the interstitial tissue, extending to every part of the cortex. The tubules show much atrophy, few being even approximately normal, and the glomeruli are all diseased, many being entirely fibrosed. On the other hand, focal nephritis, or primary chronic interstitial nephritis, is characterized by an intense but focal fibrosis of the renal cortex. In the fibrosed areas the tubules are much atrophied and the glomeruli destroyed or represented by fibrous nodes, but in the intervening areas there is only slight fibrosis, the tubules being fairly normal or hypertrophied and the glomeruli large and apparently undamaged. J. S. Dunn (Glasgow Med. Jour., Feb., 1924).

The *large red* or *variegated kidney* of *chronic hemorrhagic nephritis* forms a third variety. The kidneys are found, as a rule, enlarged, red, swelled, and congested-looking or mottled; frequently they are "bumpy," or slightly bosselated. The capsule is slightly adherent to the depressions between the bosses. The section shows congested portions and gray or yellow spots corresponding to the anemic and fatty-degenerated portions. Red spots, due to small hemorrhage, may also be noticed on both the outer and cut surfaces of the kidney, and small cortical hemor-

rhagic areas or striations, brownish red in color, are distinctive. Microscopically the appearances are those of acute nephritis superadded to those of the large white kidney, and consist of fatty granular degeneration, epithelial proliferation, atrophied capillary tufts, thickened glomeruli capsules, and, in some places, a growth of interstitial fibrous tissue. In either place inflammatory edema and cellular infiltration of the intertubular tissue may be noted, as well as the dilated tufts of capillaries with surrounding cellular hyperplasia. This variety of chronic nephritis is frequently seen in inebriates.

The majority of nephritis subjects show a more or less cloudy blood-serum during the period in which their urine contains lipoids. The only exception is nephritis from sublimate poisoning, the serum remaining clear throughout the process. The hypercholesterinemia of nephritis is probably due to the concomitant hepatic changes which prevent the physiological elimination of the lipoids. The authors detected a hypercholesterinemia in all nephritides accompanied by albuminuric retinitis. They believe this condition of the blood to be absolutely necessary for the production of the ocular complication. Kollert and Finger (Münch. med. Woch., July 23, 1918).

**Nephrosis.**—In the classification of Volhard and Fahr, which has been adopted by some American authors, the kidney diseases generally included under the term nephritis are divided into 3 groups: (a) The *nephroses*, characterized by degenerative rather than exudative changes; (b) the *nephritides* or inflammatory diseases (further described in the present section, under Definition), and (c) the *scleroses*, or arteriosclerotic diseases of the kidney.

Nephrosis has been further divided into (a) acute; (b) chronic, and (c) the terminal stage, the latter characterized by a nephrotic contracted kidney without increase of blood-pressure. As stated by Bell and Hartzell,

however, nephrosis is not sharply separable from glomerulonephritis, as the lesions of both may be combined.

The typical symptoms of nephrosis have been enumerated by R. Floyd as follows: Anasarca, excessive albuminuria, high specific gravity, no nitrogenous retention, no hypertension, no cardiac hypertrophy, practically normal dye test and test meal, pallor out of proportion to anemia, and watery stools.

The condition generally occurs in relatively young subjects. Its onset is slow and insidious, with pallor, edema of the eyelids and feet, anorexia, concomitant with the edema, and susceptibility to fatigue. The edema soon becomes widespread. The urine is scanty; it shows no blood cells, but may contain casts. The edema fluid is pseudochylous—a condition ascribed to globulin-lipoid substances. The blood serum is likewise milky; there is a high cholesterol content; the total protein content is low, but the globulin may be both relatively and absolutely increased. The course of the disease depends markedly upon its cause, the cases due to tuberculosis, long-standing syphilis or chronic suppuration, as well as those of unknown etiology, running a prolonged course, while those due to such causes as pregnancy, diphtheria and recent syphilis may exhibit a relatively acute course. On the whole, the condition is uncommon, making up only about 10 per cent. of the cases of Bright's disease.

The treatment advised by Epstein consists of a **high protein diet** (to make good the marked loss of protein from the blood), with little of the carbohydrates and little or no fats. In severe cases **repeated blood transfusions** are advocated. **Rest** and other hygienic measures generally availed of in nephritis are also indicated.

**PROGNOSIS.**—The prognosis is invariably bad, though life may, in certain cases, be prolonged. Death may occur in severe cases in from three months to a year, from uremia, dropsy, dilatation of the heart, or from other complications. Cases of a year's duration seldom recover, and those in which advanced secondary contraction of the

kidney may be assumed may be considered hopeless; they often terminate suddenly. Rarely there may be a complete recovery; this occurs particularly in children following an attack of scarlet fever. According to the quantity of urine passed in the twenty-four hours, and the amount and persistence of the albumin, is the prognosis made, as well as upon the degree of cardiovascular and retinal changes. Relapses may occur in apparently favorable cases, and acute attacks may supervene.

**TREATMENT.**—This is conducted much as in acute nephritis. The uremia and dropsy are treated symptomatically. The diet is of great moment, skimmed milk and buttermilk being depended on as much as possible when the dropsy is marked. When the dropsy is slight, more solid food, meats sparingly, eggs, vegetables, and fruits, and an outdoor life should be recommended. The reduction or complete absence of salt in the diet has a strong influence in diminishing edema. According to Foster and Davis, where there is no great amount of edema considerable water should be allowed, while the protein intake is reduced, to secure elimination of the solids and retained nitrogen.

A thorough study of the kidney function, repeated at intervals, is advisable. Edema and salt retention indicate **restriction of fluid and salt**; retention of non-protein nitrogen in the blood indicates **protein restriction**. **Water** is the mildest diuretic. **Glucose intravenously** to the point of slight glycosuria proved satisfactory. Many advanced cases develop acidosis, best combated by **sodium bicarbonate**, controlled in turn by the blood  $\text{CO}_2$  or alkalinity of the urine, to avoid alkalosis. E. H. Mason (Canad. Med. Assoc. Jour., Jan., 1923).

If a patient suffering from extreme renal edema shows a favorable blood-urea concentration and gives good re-

sults with the other renal tests, the best treatment is a good diet composed largely of **protein**. Often this increased diet may with advantage be combined with 10 to 15 Gm. (150 to 225 grains) of **urea** given by mouth twice daily. This dose may be kept up for a week, when it should be left off for a few days, to be continued at intervals for other short periods if necessary. Sometimes the edema disappears very rapidly under such treatment; if it does not, it will generally be found that the patient is not suffering from a pure hydremic condition, but shows evidence of azotemic or interstitial disease as well. In hydremic cases not very much can be done with **hot air** and other **hot baths**; they should never be used if there is any suspicion of cardiac weakness. H. MacLean (Lancet, Mar. 1, 1924).

Desiccated **thyroid gland** recommended in doses of 0.03 Gm. ( $\frac{1}{2}$  grain) 4 to 6 times a day in cases of edema without hypertension and with much albumin in the urine. This medication is to be continued for periods of 3 weeks. Fiessinger and Leboucher (Jour. des prat., Sept. 13, 1924).

Prolonged, sudden exercise and severe exercise should be prohibited. **Rest in bed** is indicated for edematous cases.

Acute glomerulitis, according to Umber, calls for an intake of fluids of about 3 pints ( $1\frac{1}{2}$  liters) daily, as failure to supply this amount favors azotemia. Should this develop, the intake should be increased; too much water, however, has been known to precipitate uremic convulsions. When the condition has become chronic, water intake cuts little figure. Dietetic excesses should be avoided.

Edema in chronic parenchymatous nephritis is ascribed by the author to the loss of protein from the blood serum through the continuous albuminuria causing a decrease in the osmotic pressure of the blood. The treatment should be to increase the protein content of the blood and to remove or cause the reabsorption by the tissues of the excessive lipoids. The former is accomplished by a

massive **infusion or transfusion of healthy blood accompanied by removal of an equal quantity of blood from the patient**, or by a high protein and fat poor diet. The latter consists of lean veal, lean ham, whites of eggs, oysters, gelatin, lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea, and cocoa, with restricted fluids and only enough salt to make the food palatable. The daily amount of calories runs from 1280 to 2500 and the daily amount of proteins from 120 to 240 grams (4 to 8 ounces); of unavoidable fats, from 20 to 40 grams (10 drams); of carbohydrates, from 150 to 300 grams (5 to 10 ounces). Other articles of food are added gradually as conditions allow. A. A. Epstein (Amer. Jour. Med. Sci., Nov., 1917).

Various examinations, correlated with metabolism studies of the same patients, showed the following: Edema plus retinal edema or low phthalein index indicates chloride retention. Elevated blood-pressure plus retinitis or low phthalein index indicates nitrogen retention. Elevated blood-pressure plus edema indicates chloride and, probably, nitrogen retention. Elevated blood-pressure plus edema plus low phthalein index indicates chlorides and nitrogen retention.

Having found out what type of physiologic renal defect a given case represents the principle of treatment is to protect the weakened function. In chloride retention the rational procedure is to limit the amount of sodium chloride ingested to within the amount the kidneys can excrete. The diet may contain fruit, milk, cereals, sweet butter, and unsalted bread: Breakfast: Apple, baked or stewed; a cooked cereal (no salt added) with cream and sugar; unsalted bread toasted, sweet butter; caffeine-free coffee with cream. Dinner: Cream vegetable soup; two eggs as omelette with tomato or onion; unsalted bread and butter; rice or tapioca pudding. Supper:

Cereal with milk; unsalted bread and butter; stewed fruit. With this method many patients show prompt improvement by diuresis and a rapid subsidence of edema.

Next, all cases of this type must be most carefully examined for foci of infection; occasionally such excellent results are secured that the chance can not be neglected.

The salt lost by nephritics from the hot pack or sweat bath is very slight in amount. Free diaphoresis will in some cases induce uremic symptoms. A **hot compress over the kidney region** will produce the same result as a hot pack and is devoid of danger and of weakening effect.

In chronic nephritis with nitrogen retention and high blood-pressure only a complete revision and rearrangement of the life and habits of the patient is beneficial. Both marked **reduction of diet** and a **curtailment of business activity** are indispensable. A surplus of **rest in bed**, i.e., much more than the conventional 8 hours, is also necessary. A low protein diet the author has used in such cases consists of a daily allowance of 1 pint ( $\frac{1}{2}$  liter) of milk, 4 slices of bread, 2 potatoes, rice, green vegetables, butter, fruit, and sugar. Taken in ordinary quantities this approximates 45 grams ( $1\frac{1}{2}$  ounces) of protein daily (7 to 8 grams— $1\frac{1}{2}$  to 2 drams—of nitrogen). In very sick patients it should be reduced.

The second principle in treatment is allied so-called "failure of concentration." It is best when commencing the treatment to give 2 quarts (liters) of fluid a day for 2 days, and collect and measure the urine each day in order to find out whether water is well excreted. If water is excreted freely then the fluid should be gradually increased up to 3 or even 4 liters per day. Where edema results from this "**forced fluid**" method, correction of this symptom can usually be effected by the use of **digitalis**. If, however, water is not well excreted, one should try the effect of

"drink days"—2 or 3 days a week when the intake is considerably augmented. A moderate amount of edema is not a sufficient reason for reduction in water ingestion. By contrast with the sequelæ of marked nitrogen retention, edema is relatively insignificant. N. B. Foster (Jour. Mich. State Med. Soc., May, 1917).

The 2 principal guides to treatment in chronic Bright's disease are the general condition of the patient as it is influenced by the progress of the affection and the rate of metabolic excretion as determined by modern methods of examination. The amount of urea excreted in the 24 hours should be carefully and repeatedly estimated. Substances which, like urea, creatinine pigments, hippuric acid, and phosphates, are excreted with difficulty should be allowed in minimal amounts. To avoid the ill effects of phosphoric acid, Von Noorden recommends that **calcium carbonate** be added to substances containing it.

A mixed diet is of advantage with proteins in quite limited amounts. Mercury in all its forms should be omitted. Sajous claims that favorable results have been reported in about one-half the cases of chronic nephritis in which **kidney preparations** were used.

One may use a maceration or, more conveniently, a tablet known as **nephritin**, 10 to 15 5-grain (0.3 Gm.) tablets daily, preferably between meals. **Salvarsan** has yielded encouraging results in cases of syphilitic origin. **Capsule-splitting** has been frequently followed by cessation of hemorrhage in chronic Bright's disease. Primary foci of infection in the teeth and tonsils should receive attention. In cases without marked edema considerable water should be allowed. When dropsy exists, the intake should not exceed a liter (quart) per diem, and a salt-free or salt-poor diet be given. **Digitalis** and the salts of **potassium**, especially the **citrate**, are safest as diu-

retics. The **Karrell diet**, which consists in giving the patients 200 c.c. of raw or boiled milk 4 times daily, at 8 A.M., 12, 4, and 8 P.M., and nothing else, is warmly advocated by some. It should be kept up for a week, then gradually relaxed. J. M. Anders (Therap. Gaz., Oct., 1917).

Various observers have called attention to **adrenalin** by the mouth as a useful agent in nephritis; 8 to 10 drops of the 1:1000 solution may be given 4 times daily. Among diuretic remedies, **theobromine sodio-salicylate** has given favorable results. Under certain conditions **calcium chloride** has also proven an active diuretic, and likewise **novasurol**.

By giving **calcium chloride** along with a salt-free diet marked diuresis can be obtained where the ordinary diuretic measures fail. The amounts the writers used ranged from 5 to as much as 19 Gm. (75 to 285 grains) a day. In some cases 11 Gm. (165 grains) a day were continued for a week. Cases of severe hydropigenous, acute hemorrhagic, and chronic mixed nephritis were included. Blum, Aubel and Hausknecht (Bull. Soc. méd. des hôp. de Paris, Feb. 3, 1922).

In 2 cases of nephritis with edema **calcium chloride** caused diuresis and loss of edema. Calcium is eliminated by the bowel and chlorine by the kidney. In certain cases sodium is freely discharged and water is made available for elimination and excreted. Keith, Barrier and Whelan (Jour. Amer. Med. Assoc., Aug. 30, 1924).

**Woolens** should be worn next to the skin, and residence in a warm, dry climate may aid in extending life.

**Nitroglycerin** may be needed in cases with contracted and tense arteries, and with a tendency to uremic twitchings; **digitalis** may be useful in cardiac weakness. **Basham's mixture** for the anemia and unirritating diuretics will prove of value, and

**strontium lactate**, in doses of from 15 to 20 grains (0.97 to 1.3 Gm.) three or four times daily, may be tried in some cases.

The writer commends the following for the management and treatment of chronic Bright's disease. In slight cases no medicine may be required, but if anemia is present an occasional chalybeate course is advisable. One of the following prescriptions may be ordered:—

**R** *Solution of ferric acetate*, B. P. . . . m̄xv (0.90 c.c.).  
*Glycerin* . . . . . ʒj (4 c.c.).

*Solution of ammonium acetate* . . . . ʒss (15 c.c.).

*Infusion of calumba*,  
q. s. ad . . . . ʒj (30 c.c.).

**M.** Take twice or thrice a day.

**R** *Reduced iron*. gr. xx (1.3 Gm.).

Pone in caps. no. xx.

**Sig.**: One three times a day.

**R** *Ferrous sulphate* . . . . . gr. iss (0.1 Gm.).  
*Magnesium sulphate* . . . ʒj (4 Gm.).

*Diluted sulphuric acid*. m̄x (0.6 c.c.).

*Peppermint water*,  
q. s. ad . . . . ʒj (30 c.c.).

**M.** Take three times a day.

The bowels must be kept moderately open. The kind and amount of aperient must be determined on general considerations. In all cases in which the arterial tension is high the author gives a mild mercurial purge at intervals of a week or ten days. The writer recommends:—

**R** *Mass of mercury* . . . . . gr. ij (0.13 Gm.).  
*Extract of euonymus* . . gr. iss (0.1 Gm.).  
*Resin of podophyllum* . . . gr. ⅓ (0.0108 Gm.).  
*Compound rhubarb pill*. gr. ij (0.13 Gm.).

**M.** et ft. pil. no. j.

A frequent symptom in all forms except the pure cirrhotic kidney is the presence of anasarca. If it is slight, it calls for no special treat-

ment; if it tends to increase, it is desirable to withdraw sodium chloride from the diet as much as possible. No salt is to be added to the food at table, and the bread and other articles of food are to be prepared without it. The following mixture may be prescribed:—

**R** *Theocine sodium acetate* . . . . . gr. v (0.32 Gm.).

*Caffeine* . . . . . gr. ij (0.13 Gm.).

*Ammonium benzoate* . . . gr. v (0.32 Gm.).

*Chloroform water*,  
q. s. ad . . . . ʒj (30 c.c.).

**M.** Take this every four or six hours.

Or, if the heart is dilated:—

**R** *Infusion of digitalis* . . . . ʒj (4 c.c.).

*Potassium citrate* . . . . gr. xv (0.97 Gm.).

*Spirit of chloroform* . m̄x (0.6 c.c.).

*Infusion of buchu*,  
q. s. ad . . . . ʒj (30 c.c.).

**M.** Take every six hours.

In cases with much dropsy the most useful medicine is the well-known Baillies pill:—

**R** *Mass of mercury*,  
*Pulverized digitalis*,  
*Pulverized squills*,  
of each . . . . gr. j (0.065 Gm.).

**M.** et ft. pil.

**Sig.**: Take every six hours.

Bradshaw (Liverpool Medico-Chir. Jour., Jan., 1910).

**Hot Nauheim baths** cause a relaxation of the entire muscular tissue, as evidenced by the fact that after taking from 4 to 5 baths patients are unable to do more than a small percentage of the walking or other exertion of which they were capable before beginning the baths. The baths also relax the peripheral circulation, and this effect may, and possibly does, extend to all tissues of the body. Nauheim baths also cause marked elimination, especially through the skin and kidneys. The writer has seen patients, who came to Nauheim with a skin almost as

dry as a sheet of parchment, after two, three, or four weeks of bathing have an active skin. The attendant increased elimination through the skin doubtless helps lessen albuminuria and lower blood-pressure. Newton (Amer. Jour. Med. Sci., April, 1912).

Physiologic rest for the injured or overworked kidney, a diet **poor in protein and in sodium chloride**, are advocated by the writer. Protein calories are replaced by carbohydrate and to a less extent by fats. Fluid intake is set at a level of about 1500 c.c. per 24 hours. The exact degree of reduction in protein, salt and fluid should vary with the degree of the nephritic process. Catharsis to give free, not loose, movements is needed for the average nephritic. Diuretics have little place in the treatment. Hypertension requires no particular therapeutics other than the diet, baths, catharsis, etc., already described. Edema in nephritis is met by reduction in fluid intake and restriction of protein and especially of salt in the diet. The high protein diet advised by Epstein (1917) for edematous nephritics, did not, in the writer's experience, give good results. The alkaline treatment of Fischer was also disappointing. Continued catharsis sometimes helps. When edema is marked, mechanical removal gives prompt, but, as a rule, only temporary relief. With a normal heart and edema from renal insufficiency, the writer has never seen diuresis from digitalis, and rarely from diuretic drugs. H. A. Christian (So. Med. Jour., Aug., 1920).

**Methylene blue** has also given satisfaction in some cases.

**NON-EXUDATIVE CHRONIC NEPHRITIS**, or **CHRONIC INTERSTITIAL NEPHRITIS**, also termed **Chronic Bright's Disease**; **Primary** or **Genuine Contracted Kidney**; **Cirrhotic Kidney**; **Red Granular Kidney**; **Chronic Productive Diffuse Nephritis without Exudation**; **Gouty Kidney**.

**DEFINITION.**—A chronic diffuse inflammation of the kidneys, indicated by a growth of connective tissue in the stroma, degeneration and atrophy of the renal parenchyma, and by marked changes in the cardiovascular system.

**SYMPTOMS.**—The symptoms may remain latent for a considerable time, even for years, while the morbid productive changes are gradually effected in the kidneys. They may not become evident until late in life, even though the kidneys may be in an advanced state of degeneration. Some complicating condition may also supervene, as pericarditis or pneumonia, causing the development of grave renal symptoms. As a rule, however, uremia makes its appearance with headache, stupor, or convulsions, dyspnea, nausea and vomiting, and a tense pulse. This seizure may be recovered from. There is now an *interim*, of variable duration, in which there are drowsiness, lassitude, a disordered digestion, headache, failing vision, dyspnea, and frequent micturition, with a more or less impaired general health. Then follows another uremic seizure, still more severe, if not fatal. If not fatal, the general health is still more reduced, and confinement to the house or bed is necessary; at last the vital forces can no longer compensate for the destruction of the renal parenchyma. Contracted kidney may sometimes first be manifested by spasmodic dyspnea (uremic; cardiac). There is a marked gradual onset of periods of drowsiness during the day that are uncontrollable; an attack of hemiplegia may be the first sign of the disease. In other cases a progressive loss of flesh and strength, with a dry, harsh, wrinkled skin, may be, from the beginning, the only clinical features, until death results from

sheer feebleness and emaciation. The variability and involvement of the symptoms render it advisable to describe them under the various systemic divisions.

There is an increase in the daily quantity of urine excreted so great that it causes a frequent desire to micturate not only during the daytime, but two or three times through the night. This may be aggravated by the hyperacidity of the urine and by the irritability of the prostate gland (especially in advanced years) that are so often associated with renal cirrhosis. The total quantity of urine for the twenty-four hours may measure several quarts in marked cases of the disease. It may be slightly decreased early in the attack, when the degeneration and destruction of the parenchyma are in their incipency; but, as the "blood-flow to the parts that remain must, *cæteris paribus*, be as great as it would have been to the whole of the organs if they had been intact," excessive pressure is brought to bear within the capillaries, owing to the compensating cardiac hypertrophy, and the secretion of the urine, especially of the watery elements, becomes more active. Diabetes may be suggested by the polyuria, but the urine is clear and pale yellow in color, the specific gravity being seldom above 1010 or 1012, and it may be as low as 1002 to 1005. Albumin occurs in traces only, or may even be absent altogether (glomerular atrophy); this condition is noted especially in the urine voided in the early morning.

The writer warns against declaring the kidneys healthy because of absence of albuminuria. A severe nephritis may exist without it. He regards albuminuria as of little value for diagnostic and prognostic purposes. Ræthery (*Médecine*, Mar., 1923).

The urea is diminished, and there is little or no sediment. On careful examination microscopically, there may be found a few casts (usually narrow hyaline), perhaps some leucocytes, and, rarely, a few red blood-cells. Late in the disease or in the presence of a uremic exacerbation or a complicating inflammation, the urine may be diminished in quantity, the albumin increased, and numerous casts be found in the more apparent sediment. Hematuria is a rare condition.

Askanazy, however, among 562 cases of chronic nephritis, found blood in the urinary sediment in 190 (35 per cent.), and in 11 of these the hemorrhage was profuse, in some accompanied by colicky pain. The diagnoses in 3 of these cases were confirmed at autopsy, and in all the clinical symptoms were characteristic of chronic nephritis. The hematuria and colicky pains sometimes observed in nephritis are so typical of stone in the kidney that they may be very misleading. Profuse hematuria occurs likewise in tumor and tuberculosis of the kidney.

Severe *hematemesis* observed in a personal case, due, as far as could be ascertained, to chronic nephritis with hypertension. A review of the literature furnished several reports of this unusual complication, but gave no uniform conclusions about its cause or pathology. H. F. Shattuck (*Amer. Jour. Med. Sci.*, Feb., 1923).

Epistaxis may occur and constitute a serious symptom.

Sudden edema of the larynx may also supervene, and is always a grave condition. Transudations into the pleural sac (hydrothorax) and the lungs may precede the fatal termination. Dyspnea is either uremic or cardiac and is usually worse at night; a true orthopnea, with Cheyne-Stokes breathing, may be observed in association with uremic stupor and coma, and near the end of the patient's life.

The signs of hypertrophy of the heart



(particularly of the left ventricle) may be elicited, though symptoms referable to the heart itself are absent, unless dilatation and feebleness, sudden arterial contraction, or endocarditis occur. Inspection and palpation show the apex-beat to be displaced downward and to the left, and the impulse to be increased, heaving, and rather circumscribed. In cases of coexisting emphysema, and later, when dilatation may eclipse the hypertrophy, these signs may become less evident. The left border of deep cardiac dullness extends outside the nipple-line in the fifth or sixth interspace.

In 14 cases of chronic nephritis with azotemia, but *without hypertension*, and with no hypertrophy of the heart, nervous disturbances were frequent. The azotemia is generally moderate and the Ambard coefficient is high. The amount of uric acid in the blood ranged from 0.007 to 0.015 per cent., reaching 0.028 in 1 case. This form of nephritis is often a result of old or congenital *syphilis*. Laroche and Desmoulière (Presse méd., Aug. 20, 1924).

The first sound of the heart is loud and may be reduplicated. Accentuation of the aortic second sound is a distinctive sign, and indicates increased vascular tension; it may have a metallic quality in some cases. There may also develop a mitral systolic murmur as the result of relative insufficiency. There is increased tension of the pulse, the latter being hard, persistent, and incompressible; the pulse-wave is also increased in duration (*pulsus tardus*). The systolic blood-pressure is decidedly elevated, often exceeding 200 mm. Hg. Most of the palpable arteries are hard, thickened, and tortuous, owing to the arteriosclerosis.

Gastric symptoms are among the most common early symptoms of nephritis. In cases with obscure

gastric disturbances, chemical examination of the blood was found very valuable. Several cases are reported in which estimation of the blood creatinin not only showed the patient had severe nephritis but gave a fatal prognosis. In some of the earlier cases the blood uric acid was of value as an early diagnostic sign. A. F. Chace (Amer. Jour. Med. Sci., June, 1917).

Senile nephritis causes many symptoms in other organs, while giving little evidence of renal disease. Minor symptoms which may become severe and classed as complications are "dead fingers," cramps in the calves of the legs, deafness, a sensation of electric shock on lying down, sensitiveness to cold, and nocturnal micturition. Uremia may affect one organ only, as in gastric, renal, or cerebral uremia. Other complications are indigestion, gastrointestinal disorders, pyorrhea alveolaris, neuritis and neuralgia, cerebral symptoms, and uremic fever. Many of these conditions improve when attention is given to the diseased kidneys. The urinary picture may be clear on some days and obscure or entirely hidden on others. M. W. Thewlis (Med. Rev. of Rev., Sept., 1918).

As soon as compensation fails, symptoms of breathlessness on exertion, palpitation, and the like appear; often these occur in paroxysms and constitute "cardiac asthma." The resulting stasis causes a transudation into the lungs (bronchorrhea, pulmonary edema) and later to edema of the extremities.

Since they are indicative, as a rule, of grave uremia, the symptoms referable to the nervous system are of great importance. There may be neuralgic pains throughout the body, especially of the calf muscles, and insomnia, and cephalalgia is frequent. Later great drowsiness is often a premonition of uremic coma. Muscular twitchings may precede convulsions, and should attract

attention to the imminent danger. Cerebral apoplexy with hemiplegia may form the first symptom of contracted kidney, and is apt to occur in cases of marked hardening and weakening of the arteries. Hemorrhagic pachymeningitis and hemorrhage into the brain-substance may also occur. The hemiplegia may last until the end, or it may disappear soon and be followed by subsequent attacks at intervals. Dieulafoy regarded numbness, formication, and pallor of the fingers ("dead finger") as possible early signs of chronic Bright's disease.

Many cases of interstitial nephritis with muscular twitchings or convulsions showed blood calcium values below 7 mgm. per 100 c.c. of serum. In individual cases there was a gradual fall in calcium with a rise in the inorganic phosphorus. There was, however, no uniform inverse relationship between the level of the inorganic phosphorus and the calcium in different cases. Inorganic phosphorus retention seems to be a reliable prognostic sign in chronic nephritis, though creatinin retention is equally reliable and seems to occur a little earlier. Schmitz, Rohdenburg and Myers (*Arch. of Int. Med.*, Feb., 1926).

Of the symptoms referable to the special senses nephritic retinitis often forms the earliest evidence of chronic Bright's disease. There may or may not have been present a slight dimness of vision prior to the ophthalmoscopic examination. There is a partial loss of vision in both eyes (amblyopia), and in grave cases sudden and complete blindness may come on (uremic amaurosis) as the result of a neuroretinitis. The optic papilla is swelled and surrounded by retinal hemorrhages or by white dots and streaks ("feather-splashes").

Barker and Hanes have called attention to the frequency of exophthalmos and the allied ocular signs—*anisocoria*, *von Graefe's*, *Moebius's*, or *Stellwag's* signs—in chronic

nephritis. All cases with albuminuric retinitis showed it. High pressure and exophthalmos are but evidences, according to these observers, of poisoning by perhaps separate toxins.

According to Rachlis, pigmentation of the retina in nephritis sometimes occurs from degenerative changes of the external and middle retinal layers.

Papilledema was seen by the writer as the sole ocular manifestation of nephritis with high blood-pressure. More often, however, it was associated with retinal changes. The choked disk is to be regarded as a simple consequence of the increased intracranial pressure in such cases. Larsson (*Zent. f. inn. Med.*, June 6, 1925).

There is, as a rule, no edema in renal sclerosis, and when it does occur (as in the ankles and limbs) it is due to cardiac dilatation and failure. The skin is dry, and the pores sometimes appear lustrous with minute scales of urea. The skin has often, also, a cyanotic tinge, with a certain degree of pallor. Troublesome eczema and pruritus are often present, and muscular cramps may make the patient still more uncomfortable; the latter occur at night and especially in the calves of the legs. Other cutaneous disorders may also occur.

Debility and emaciation become extreme with the gradual failure of the general nutrition.

Uremia may supervene at any time, and may even form the first symptom; it may also be sudden and severe in its attack (acute uremia), or gradual, mild, and insidious (chronic). These uremic attacks may be accompanied either by a normal temperature or by moderate fever; the temperature may even be subnormal in chronic uremia with prostration, coma, a feeble pulse, and delirium. Uremic diarrhea may also occur.

Among the complications that may occur in the red, granular, and con-

tracted kidney are the following: Pleuritis, endocarditis, pericarditis, cerebral hemorrhage, endarteritis; pneumonia, either lobar or lobular; laryngitis, bronchitis, hepatic cirrhosis, gastritis, enteritis, peritonitis, meningitis, emphysema, phthisis, and mental disorders.

A diagnosis of chronic interstitial nephritis is warranted on the basis of a persistent slight albuminuria, with casts, and the passage daily of large amounts of clear, pale urine of low specific gravity. The earliest indication of diminished renal efficiency is, however, probably given by the *test-meal for renal function* of Mosenthal and Lewis, carried out thus:

The patient eats 3 full meals a day—at 8 A.M., 12 M., and 5 P.M.—and notes down the approximate amounts taken. No food or fluid is taken between meals. The urine is collected every 2 hours from 8 A.M. to 8 P.M., while the urine passed between 8 P.M. and 8 A.M. constitutes the night specimen. In a normal test there is recorded a maximum specific gravity of 1018 or more; the specific gravity varies 9 points or more from the highest to the lowest, and the night urine measures 400 c.c. or less and is of high specific gravity—1018 or over. Reduced renal function is indicated by lowering of the maximal specific gravity, with fixation of the specific gravity and nocturnal polyuria.

The prognosis and duration of renal disease may be foretold from the urea content of the blood. In the premonitory stage the urea content of the blood is within normal range. In the second it ranges from 0.50 to 1 Gm. This initial azotemia may retrogress, but often it persists a very long time or passes rapidly into the next stage. As long as it has not passed beyond 1 Gm., the organism seems to adapt itself to it and it is impossible to foretell the duration of the disease. Life can be maintained without apparent disturbance even when only a minimal portion of the parenchyma is left. But when re-

peated examination shows that the azotemia is permanently above 1 Gm., the condition is extremely grave, and when 2 Gm. is reached and passed, a fatal termination impends. Widal, Weill and Vallery-Radot (*Presse Méd.*, May 23, 1918).

The *urea concentration test* has been warmly recommended by MacLean, de Wesselow, Barber and others. After voiding, the patient ingests 15 Gm. of urea in 100 c.c. of water and passes urine after 1 and 2 hours. Both specimens being tested for urea percentage, the higher one is taken as the result of the test. Healthy kidneys should pass 2.5 to 4 per cent. of urea; a reading below 1.5 is definitely poor. The test proved of value, in Barber's experience, in accidental or physiologic albuminuria (being then negative), leaky kidney, chronic nephritis, renal dwarfism, toxemia of pregnancy, and acute and subacute nephritis, in which the urea elimination increased as the patient's condition improved.

The balance between urine output and fluid intake should normally range from 2:3 to 3:4. Renal function should be tested in the following way: If it is not evident that the nephritis is very mild, the phenol-sulphonphthalein test should be performed and blood taken from the arm before breakfast for chemical analysis. Urea determination is easier and perhaps more instructive than the total non-protein nitrogen determination. If these tests give approximately normal results, they should be followed by the 2-hour or concentration test—which, in the case of an obviously mild nephritis, is done at the outset. All tests should be repeated, and the emptying of the bladder should be checked by catheterization where there are discrepancies between the blood nitrogen and phthalein excretion values. H. A. Christian (*New Orl. Med. and Surg. Jour.*, May, 1924).

**ETIOLOGY.**—Sometimes the cause of the slow, primary, diffuse degenera-

tion, atrophy, and fibroid contraction of the kidneys is quite obscure, and in certain cases it would seem to be "only an anticipation of the gradual changes which take place in the organ in extreme old age" (Osler)—the "senile kidney." Heredity undoubtedly plays a part in the causation of certain cases, and its influence has extended down through the third and fourth generations.

Age and sex also exert an influence, the disease being more common in males than in females, and usually beginning near middle life. It is rarely manifested symptomatically until the fiftieth or sixtieth year. A special tendency to sclerotic degeneration of the arteries, from whatever injurious influence, whether chemico-toxic or parasitic, renders the patient more prone to interstitial nephritis, though prolonged irritation by such agents may also cause the disease in persons whose cellular nutrition is usually not defective. Alcoholism, uric acid, and lead, giving rise to chronic poisoning, have all been assigned as causes of the disease.

Chronic malaria and syphilis also probably exert a causative influence.

Habitual overeating and overdrinking no doubt frequently cause granular atrophy and sclerosis of the organ, owing to the imperfect assimilation of the substances ingested and the constant excretion of irritating products by the kidney caused thereby. A widespread cause of the disease is the continuous and even moderate use of alcohol for many years; especially is this true in the case of spirituous liquors. The excessive use of meats in the diet may lead to the production of the renal disorder by deranging the hepatic function (Murchison).

Gout may also cause chronic Bright's

disease, and is allied to the above; this occurs perhaps more frequently in England than in this country, where lithemia and nervous dyspepsia are more often seen.

According to Strümpell, severe articular rheumatism is sometimes followed by contracted kidney.

Anxieties, worries, and the high nervous tension required by modern business activity and by social life (the latter, particularly, in elderly ladies) favor the development of chronic Bright's disease. Associated with these causes are usually to be found an over-indulgence in rich foods and sedentary habits.

The cold, moist climate of New England and the Middle States has been stated to predispose to contracted kidney. Hydronephrosis, chronic pyelitis, and chronic congestion of the kidney (of cardiac origin, etc.) may cause a chronic productive nephritis without exudation, though never the true "contracted and red-granular" kidney.

Stress laid on examination of the intestines in renal disease of obscure origin. It is useless to treat the kidney and leave the intestinal focus. Suppurative processes in the kidney and bladder are readily recovered from unless the intestinal focus perpetuates them. Lemierre (*Médecine*, Mar., 1920).

Bacilli of intestinal type in pure culture were obtained from the urine of patients with idiopathic nephritis. Injection of these into animals induced nephritis, and the organisms were recovered from their kidneys. In human cases, treatment with appropriate vaccines caused rapid improvement. Day and Clarke (*Lancet*, Sept. 11, 1920).

Animals fed on a high protein ration for prolonged periods showed nephritic changes, without exception. While there are other factors of nephritis, it seems very possible that the high protein ration generally used by people in

temperate zones is a definite cause. N. Evans and E. H. Risley (Cal. and West. Med., Apr., 1925).

**PATHOLOGY.**—The reduction in size and weight is about equal in both organs in genuine primary contraction of the kidneys. The two kidneys may together weigh not over two ounces, and they may be only one-half or one-third the normal size. They are frequently imbedded in thick adipose tissue, and the capsule is thick, opaque, and very adherent; so that, on stripping it off, portions of the renal cortex come away at the same time. The outer surface of the organ is red, irregularly granular, or finely nodular, and occasionally small cysts are present. The tissue is firm, dense, and resistant to the knife. The cut surface shows a thin, atrophied cortex, with dark-reddish streaks alternating with pale portions. The pyramids are darker than the cortex, and are also diminished. In the gouty contracted kidney they show fine striations of sodium urate or of uric acid, or crystals representing uric acid infarctions. The principal changes are seen microscopically to be an increased production of connective tissue, especially in the cortical substance, and a more or less proportionate degeneration and atrophy of the renal parenchyma. The destruction of the latter is due to the circulation of noxious agents, but it is replaced by cicatricial fibrous tissue (Weigert). This new tissue is not uniformly distributed in the cortex, but appears in irregular masses around the shrunken glomeruli or between the tubules. In the pyramids the distribution is more general. The glomeruli are, in many instances, very small and fibrous in advanced cases; in the earlier cases the cells of the tufts and capsules are swelled and multiplied and a small-

celled infiltration may be seen around the glomeruli and tubules. This cellular infiltration later becomes fibrillated and ends in thickening.

The changes that take place in, and the growth of the capillary and intracapillary cells and of those around the tufts are partly responsible for the glomerular atrophy, as are also the capsular thickening and hyaline or waxy degeneration and the thickening and occlusion of arterioles. The tubules show decided changes, some being included in masses of connective tissue, with resulting compression-atrophy and even obliteration of the lumen. Others show constriction by the intertubular connective tissue, the lumen elsewhere thus being increased; this is especially prominent in the granules on the outer surface of the kidney, and little cysts may be seen here and there by the naked eye, as the result of damming back the urine in the tubules thus affected. The epithelium lining these tubules shows granular, fatty, or waxy degeneration, and may be either flattened, cuboid, or swollen in variety. The tubes may contain fatty or granular *débris* and tube-casts.

Aside from the true red granular kidney, three other pathologic forms are recognized which may be grouped under the present heading:

(a) The *arteriosclerotic kidney*, which is red and dense, but not much reduced in size, being, in fact, frequently heavier than normal. The surface is smooth, and the capsule but little thickened and only slightly adherent. Localized atrophic changes may be found in certain cases, manifested in red, depressed areas. The cut surface of the arteriosclerotic kidney is reddish brown and presents arteriosclerotic vessels, featured by obliterating endarteritis. In

this form the arteriosclerosis is held to be the primary pathologic factor.

The arteriosclerotic kidney results from atheroma and other senile changes in the renal arteries, so that portions of the kidney substance undergo atrophy. It is met with chiefly in persons over 60 years of age, and the albuminuria by which its existence is recognized is often associated with evidence of disease in the vessels of organs other than the kidneys. T. K. Monro (Glasgow Med. Jour., Feb., 1924).

(b) The *senile kidney*, in which the organ is reduced in size and shows an increase in the pelvic fat. The capsule is thickened and adherent, both the cortex and pyramids decidedly atrophied, and the arteries sclerotic.

(c) The *secondarily contracted kidney*, or small white kidney, already described under Chronic Exudative Nephritis.

In the classification of Volhard and Fahr, which is in agreement with certain conclusions reached by Ophuls a number of years ago, what is commonly termed chronic interstitial nephritis is included in a major group characterized as the arteriosclerotic diseases or sclerosis of the kidneys (apart from the nephroses and nephritides) on the basis of the view that the primary contracted kidney is actually the result of an arteriosclerotic process of the smaller vessels of the organ and is not at all an inflammatory condition. The renal sclerosis are divided by these observers into 2 subgroups: (1) *Benign hypertension*, considered as identical with "essential hypertension," Allbutt's "hyperpiesia," and the red granular kidney, and (2) *malignant hypertension*, consisting of a similar renal vascular sclerosis plus a gradual, progressive chronic glomerular nephritis.

In "benign hypertension" the renal functions are described as undiminished. The clinical features are cardiovascular, with hypertension (at first sometimes intermittent), marked left ventricular hypertrophy, gradually increasing myocardial insufficiency, good general health at first;

absence of anemia (often polycythemia instead); urine normal or with but little albumin and a few casts; frequently nocturia; arteriosclerotic, but not nephritic, retinal changes; absence of true uremia with azotemia. The patients are generally over 50 years. The condition is regarded as curable at first, and later subject to arrest or prolonged palliation.

In "malignant hypertension" the cardiovascular manifestations are similar to those of the preceding condition, but more pronounced. There is failure of general health, passing into nephritic cachexia. An especial feature distinguishing it from the benign type is functional impairment of the kidneys; the presence of papilledema and neuroretinitis is likewise diagnostic. There is pronounced anemia. Death may occur from the circulatory condition, infection, or true uremia resulting from the glomerular nephritis.

The writer presents a pathological study of 1000 consecutive cases. The so-called primary or genuine contracted kidney represents a disease which is the result of arteriosclerosis in the terminal arterioles of this organ and is closely associated with general arteriosclerosis. There is some reason to believe that the condition as a whole is a toxic one. So far, however, lead is the only substance which seems to bear any definite etiological relation to the general process. Of true primary subacute and chronic inflammations of the kidneys there remain subacute and chronic glomerulonephritis, definitely, in the majority of instances, due to chronic sepsis. Closely related to this, etiologically and anatomically, is the subacute and chronic amyloid kidney (the large, white kidney of other authors). From a combination of the last two conditions there arises the so-called secondary contracted kidney, which, in the author's series, was responsible for 11 out of 37 cases of seriously contracted kidneys. Ophuls (Archives of Intern. Med., Feb., 1912).

Stress laid on the quantity and biologic value of the albumin circulating in the blood as factors in the production of edema. Retention of

chlorides alone is not enough to account for edema. The blood serum must be in a condition permitting dialysis, and this occurs when its albumin content is below normal from any cause, permitting the transudation through the capillary wall. As edema subsides, the albumin content is found higher, and *vice versa*. The albumin is the regulator and index of the osmotic balance, and the integrity of the liver is indispensable to keep the albumin content normal. The lung being the largest dialyzing membrane in the body, any abrupt change in the osmotic balance is liable to entail intense dialysis here, resulting in acute edema of the lungs. The author cites cases showing the fatal import of abnormally low albumin content in the blood serum. One woman with fatal chronic nephritis had an albumin content always below 0.1 per cent. Facio (*Semana Medica*, Apr. 19, 1917).

In severe nephritis there is high fat in plasma and corpuscles and high lecithin in the corpuscles. These abnormalities are the same as are found in alimentary lipemia and for this reason are probably the result of a retarded assimilation of fat in the blood, which in turn, is thought to be due to a general metabolic disturbance brought about by a lowered "alkali reserve" of the blood and tissues. W. R. Bloor (*Jour. Biol. Chemistry*, Sept., 1917).

Cardiac hypertrophy is an almost constant attendant upon chronic, non-exudative, productive nephritis, and its degree depends upon the extent of the renal, and also of the general arterial, degeneration and sclerosis. *Cor bovinum* has been applied to the organ, on account of its extreme size in this affection. The left ventricle only is hypertrophied in moderate enlargements.

According to Bouveret, 93 per cent. of all cases of interstitial nephritis are accompanied by enlargement of the heart. There are some exceptions, however.

Some conditions prevent the occurrence of the cardiac enlargement, viz., advanced age, tuberculosis, and cachectic states. Again, there occur cases with greatly contracted kidneys, uremic attacks, and death, without cardiac enlargement. These cases are nearly always chlorotic and anemic, with vascular aplasia or a badly developed condition of the heart and vessels. Lancereaux was the first to point out that in badly developed states of the vascular system renal sclerosis does not cause enlargement of the heart.

According to Mayet the only rational theory explaining the frequent coexistence of nephritis and hypertrophy of the heart is that of reflex action: between the glomerular arterioles and the innervation of the heart and vessels there exists an intimate reflex relationship whereby the least constriction of the arterioles reacts upon the vasomotor nerves.

Discussing the pathogenesis of the cardiovascular syndrome in renal disease the author points out that the urinary secretion is the product of an automatic function with a general vasoconstrictor action, and a local vasodilator action for regulating the excretion of the metabolic wastes. In the case of the lungs, the lesser circulation must always give passage to the same quantity of blood, so that in case of obstruction the blood-pressure must be increased and the right heart must enlarge in proportion to the work to be done. The left heart in turn becomes enlarged. The same state of affairs is seen in the kidneys. Just so much blood must be depurated in a certain interval, and if obstruction to the local circulation is present the volume of the heart is increased and a polyuria develops. In the course of a chronic nephritis there occurs an alternation of periods of insufficiency and periods of complete function; this is maintained until there is reached a stage of permanent insufficiency. Silvestri (*Riforma Medica*, Jan. 6, 1917).

Three cases of *malignant hypertension nephritis*, or *primary sclerotic kidney*, in children, all of whom died within a year after the onset. There

was little complaint, except of weakness and malaise, until the renal insufficiency was far advanced, when headache and vomiting appeared. There was marked abdominal pain, of undetermined origin. Urine output was greater than fluid intake. There were polyuria and fixation of specific gravity at a low level, with a little albumin and a small number of hyaline and granular casts. The blood in one case showed a moderate increase of nitrogenous elements; in another, marked retention. In the third, phthalein output was practically *nil*. Hypertension was marked and constant. There was anemia in one case and arterial thickening in 2. There was moderate left ventricular hypertrophy and also ocular findings similar to albuminuric retinitis. H. Schwarz (Amer. Jour. Dis. of Childr., Mar., 1924).

A reduction of total base and an increase of undetermined acids are the chief factors of *acidosis* in chronic interstitial and arteriosclerotic nephritis, phosphate playing a somewhat less important rôle. The acidosis seems greatly influenced by variations of plasma chloride. Bulger, Peters, Eisenman and Lee (Jour. of Clin. Invest., Feb., 1926).

Certain complications, *e.g.*, cerebral hemorrhage, cirrhosis of the liver, pulmonary emphysema, chronic endocarditis, chronic endarteritis, bronchitis, and gastric catarrh, may exist.

**PROGNOSIS.**—Chronic interstitial nephritis varies in duration, and in uncomplicated cases it may last for five, ten, twenty, or possibly thirty years. The duration may, however, be very much shortened by complications or intercurrent affections, or the condition may not be appreciated, as often occurs, when the post-mortem examination discovers the characteristic kidneys in one who had no symptoms of renal disease during life and whose death was directly due to some intercurrent affec-

tion. Life is destroyed sooner or later by this disease, unless the patient first dies from some intercurrent malady. Irreparable damage to the organs results from the gradual destruction of the renal parenchyma and its replacement by scar-tissue. The fact, however, that the process is slow, and its duration, therefore, long, allows a preservation of life for many years, and often with comparative comfort. The prognosis depends much upon the general condition of the patient, the cardiovascular system, and upon the presence of uremia and inflammatory complications. A not far distant end is indicated by cardiac dilatation and insufficiency. Hemorrhages, diarrhea, persistent vomiting, nephritic retinitis, coma, and delirium render the prognosis exceedingly grave. Convulsive and apoplectic seizures are often fatal.

The various functional tests are of considerable prognostic value. As the renal insufficiency progresses, phthalein elimination decreases, and the blood urea and uric acid increase. In the terminal stages, phthalein may not be excreted, the blood nitrogen ascends very high, salt and lactose are retained, and the urinary specific gravity is fixed and constant. The blood creatinin may rise to over 5 mgm. per 100 c.c. of blood when death is imminent.

In 20 normal persons the blood creatinin ranged from 1 to 2.5 mgm. per 100 c.c. of blood. In cases of chronic nephritis the figure exceeded 2.5 mgm. When the range was between 2.5 and 5 mgm. the patients improved under treatment. A creatininemia above 5 mgm. was frequently, but not inevitably, soon followed by death. Costa (Lisboa med., i, 557, 1924).

**TREATMENT.**—A strict hygienic *régime* following an early appreciation



of the disease will, to a considerable degree, prevent the advance of the cirrhotic process. Noxious substances that have an etiological influence must be removed as thoroughly as possible. Alcohol is interdicted, and lead—when the causative factor—must be prevented from further poisoning the system by a change of occupation. The heart and blood-vessels are also preserved by the diminution of these irritants. The hygienic treatment embraces a regulation of all the habits of the body and the mode of living. The malady is incurable; therefore, the patient himself must be treated, and not the malady. A suitable dietary must be formulated for each individual. An absolute milk diet may be necessary for short periods in the presence of gastric irritability, but undue weakness will be the result of a continued restriction to milk alone.

In chronic nephritis the food should be simple. Pies and other pastries, fried food, and all complex, highly seasoned dishes should be interdicted. To avoid constipation, the diet should include always a sufficient amount of honey, fruits, vegetables, bran and other laxative foods. J. S. McLester (So. Med. Jour., Mar., 1923).

The diet in chronic interstitial nephritis must be guided by the extent of the lesion and the state of renal function. When the case is very advanced, the usual **low protein diet** is probably best, but in many patients experience shows that the custom of prescribing a very low diet does harm. In such patients a marked improvement in general health can frequently be brought about in a few weeks by allowing a good diet containing a fair amount of protein. No doubt the tendency to anemia is frequently due to an insufficient diet. H. MacLean (Lancet, Mar. 1, 1924).

A light, nourishing diet is, therefore, advisable. Lean meat may be allowed once daily in favorable cases; eggs,

vegetables, greens, fruits, and light, well-cooked, farinaceous articles may also be partaken of. Tea, coffee, and cocoa may be drunk in moderation. The use of the natural mineral waters aids in the renal circulation and keeps the kidneys flushed. As a rule, a mixed diet will be advantageous. The nitrogenous and carbohydrate elements (sugars and starches) should be used in moderate amounts, but fruits and pure fats are to be recommended. Where a milk diet is to be used, Von Noorden has recommended 3 pints of milk mixed with 1 pint of cream daily, to reduce the excess of protein in milk alone.

In aged nephritic patients 6 to 20 tablets of **extract of kidney of a pig** seemed to give good results and check the process of degeneration. **Cabinet baths** are useful, particularly in the corpulent and those with much headache, but in the aged caution is required. The **elixir of iron, quinine, and strychnine** usually works well as a tonic after the eliminative treatment. It is well to keep old people out of bed and to have them work. M. W. Thewlis (Med. Review of Rev., Aug., 1917).

In chronic nephritis efforts to spare the kidney are useless. The writer always gives a full diet except for a reduction of the purin group. Red meats are no worse for nephritis than white meats, but if the patient is told he can eat white meat and nothing else he soon gets tired of eating white meat, and a reduction of meat is thus accomplished indirectly. Meat soups should be forbidden. Salt is not altogether excluded. Patients complain bitterly against not having salt added to the cooking, but get along very well without adding any at table. **Daily exercise** is essential for the support of the muscular power of the nephritic heart. Drugs and **high frequency electricity** will reduce the systolic blood-pressure, but almost never

the diastolic blood-pressure. R. C. Cabot (Med. Standard, Oct., 1917).

The first step in any type of kidney disease is to **eliminate focal infections**, as in the tonsils, crowned teeth, and diseased prostates.

In the cardiorenal type, the next most important measure is **rest**, both mental and physical. If the patient has good functional kidney capacity he should be put on a low, general, simple **diet**. He should be allowed to have some meat and eggs.

In the clinical type with edema and much albumin, when severe, **rest** and a limited milk fluid **diet** as first suggested by **Karell** are best. The author prescribes for the first few days 1 quart (liter) of milk, 1 pint (500 c.c.) of water, and either another pint of **lime water** or some **salt of calcium**, either the **carbonate** or **lactate**, in 0.5 Gm. (7½ grains) doses several times daily. **Tincture of iron** or **ferrous carbonate** is also given.

In the type with no albumin, fairly normal renal functional capacity, and few symptoms, the **diet** should be more liberal and contain a large amount of protein. As many as 8 to 10 ounces (240 to 300 Gm.) of meat might be very helpful. **Fluids** should be **restricted**. If there is evidence of salt retention its use should be curtailed, otherwise it may be sparingly permitted. J. R. Williams (N. Y. Medical Jour., July 20, 1918).

A **free fluid intake** is beneficial in almost all cases of kidney disease. Lowering the water intake does not "rest the kidney," but puts additional strain on its delicate concentrating function. O. H. P. Pepper (Penna. Med. Jour., Nov., 1922).

Importance of **diet** in chronic nephritis emphasized, *viz.*, a low-protein, moderately high fat and carbohydrate diet, with an abundance of water. It must include all the vitamins; in fact, the antiscorbutic **vitamins** in oranges, grapefruit and lemons are absolutely essential for the maintenance of the appetite, to say nothing of their specific action. Treatment by drugs is the least important part of treat-

ment. With diet, reduction of the salt, **exercise**, **baths**, **massage**, and **sunlight**, drugs seem to be quite unnecessary, except, perhaps, **iron**, **mild laxatives**, and occasional **refrigerant diuretics**. Warfield (Jour. Mich. State Med. Assoc., Sept., 1924).

Investigation showing the effect of a **low sodium chloride diet** in lowering blood-pressure, even in the absence of apparent renal damage. In chronic interstitial nephritis a reduction of the salt is helpful, while a large amount of salt is injurious. In the various types of nephritis examined, the ability to excrete chloride was least in secondarily contracted kidney, somewhat better in chronic interstitial nephritis, and but slightly subnormal in hyperpiesis. Satisfactory results are obtained when the quantity of salt taken is reduced to 2 or 4 Gm. (½ to 1 dram) a day for a couple of weeks, then increased somewhat. E. G. B. Calvert and S. W. Lane (Pract., Sept., 1924).

Persons who take considerable exercise may have a larger amount of food than those who are stout or who lead sedentary lives. Gastric disorders require a liquid diet until the digestion is restored, or the elimination of all but the soft and bland foods. All extremes of activity (bodily, mental, and emotional) are to be avoided.

Stress laid on the **removal** of such causes as **infected tonsils**, **teeth and sinuses**, **acute syphilis**, **septicemia** or **chronic suppuration**. The author emphasizes the acidity of the body fluids in nephritis, and to counteract it, advises a **basic diet**, *i.e.*, especially the vegetable foods, nuts, and fruits except prunes, plums, and cranberries. Neutral foods, such as butter, corn starch, cream, sugar, lard, and tapioca may be used, but many of the acid foods, such as bread, eggs, fish, meat, and cereals should not be used, except that bread and cereals may be allowed in specified amounts. Routine hydrogen ion concentration estimations are made on 24-hour urine

specimens by Clark's simple colorimetric method, a pH of 7 or better being considered satisfactory. *San-sum* (Cal. State Jour. of Med., June, 1922).

Physical **exercise** should be moderate and regular, and, if the climate be warm and dry, it should be taken in the open air. The patient should never be subjected to the vicissitudes of worry, anxiety, or to the tension of competition. Indulgences of whatever nature, if they tend to unbalance self-control or disturb the equanimity of the patient, must be strictly prohibited.

Often life may be prolonged by a change of residence to a warm, dry, and mild **climate**, since the variability and humidity of temperate climates, particularly during the winter season, tend to aggravate the disease. A sea-voyage or a sojourn at some southern, western, or southern European resort may be very beneficial.

Medicinal treatment is employed for the following indications: The bowels should be kept free by the assistance of **laxatives** or by **laxative alkaline mineral waters**. Digestants, with bitter tonics, are useful in cases of furred tongue and indigestion. Acids or alkalis, according to their special indications, may also be used simultaneously.

High vascular tension is to be met by the cautious use of **nitroglycerin** in gradually increasing doses, beginning with 1 minim (0.06 c.c.) three or four times daily, until all danger of rupture of the vessels is over.

In the early cases the writer recommends **rest in bed** for a week or two if the blood-pressure is high; this will often lower the pressure from 220 or 240 to 160 or 180. Success in treatment depends upon teaching the patient to recognize his limitations and readjust his activities and diet. In the cases troubled with headache, dizzi-

ness, palpitation and shortness of breath, the period of rest in bed, with **bromides**, 15 grains (1 Gm.) 3 times a day, seldom fails. The **diet** during this rest should be **low protein, low salt and low purins**, i.e., with omission of meat soups, tea, and coffee. The absolute amount of food is also restricted. For severe headache and dizziness, **tolysin**, 5 grains (0.3 Gm.), or **cinchophen**, 7 grains (0.5 Gm.), is frequently valuable. **Venesection**, 300 to 500 c.c. (10 to 16 ounces), often gives relief. Some cases, seemingly requiring **morphine**, obtain rather lasting benefit from **lumbar puncture** plus venesection. As long as there is no nitrogen retention, meat, poultry and eggs may be allowed to such an extent that the urinary nitrogen does not exceed 10 to 12 Gm. a day. Edema of the legs yields to rest in bed. Oliguria and nervous symptoms do not always mean uremia. If there is not a marked increase of blood uric acid, urea and creatinin, the heart is at fault and vigorous **digitalis** or other cardiac treatment is required. **Diuretin**, 20 grains (1.3 Gm.) 2 or 3 times a day, may raise the urine output from 200 to 2000 c.c.

In the last stages of nephritis, the writer advocates **digitalis** cautiously, no diuretics, **frequent purgation** with **magnesium salts**, and **hot packs, hot air baths, or electric baths**. The many cases that perspire only with difficulty should be carefully watched; if they fail to perspire, heat treatment should be abandoned or  $\frac{1}{10}$  grain (0.006 Gm.) of **pilocarpine** tried to start perspiration. In uremic cases, **bromides, chloral hydrate, cinchophen, and sodium salicylate** greatly assist in controlling the symptoms. When coma sets in, **venesection**, followed by **infusion** of 5 or 6 per cent. **glucose solution**, 300 to 500 c.c., often gives satisfactory results, along with **diaphoresis** and **purgation**. A. I. Ringer (*Amer. Jour. Med. Sci.*, June, 1921).

The other extreme, of a very low tension that induces dropsy and complications, usually uremic (convulsions, dys-

pnea, and headache), also calls for therapeutic assistance. Headache, vertigo, and so-called "renal asthma" are also often relieved by **nitroglycerin**.

Low tension, with scanty albuminous urine, edema, and signs of dilatation, requires heart tonics and stimulants, in conjunction with purgatives. **Digitalis** is effective, especially in the infusion, combined with **strychnine nitrate** or with **citrated caffeine**. The dropsy calls for the **salines**.

In advanced cases of *cardionephritis with edema*—myocarditis, cardiosclerosis, and coronary disease, alone or in combination, with edema of the legs and thighs, general anasarca, secondary hydrothorax and bronchitis, ascites, pulmonary and hepatic congestion, the writer has found **novasurol** useful or even life-saving, especially when the usual digitalization and diuretics have failed. The drug is chemically a double salt of oxymercurichlorphenoxyl sodium acetate and diethyl malonylurate, contains about 33 per cent. of mercury, and may be given intramuscularly or intravenously in aqueous solution. It is a powerful diuretic, acting usually within 24 hours, with resulting reduction of edema, visceral congestion, dyspnea and the semistupor from cerebral edema. The 2 contraindications to it are acute glomerulonephritis and enteritis. Good care of the teeth and gums must be taken during its use, and the intake of food and fluid preferably restricted for a few days. S. Neuhof (Ther. Gaz., Jan., 1924).

Uremic symptoms are to be managed, as in acute Bright's disease, by means of free **catharsis** and profuse **sweating**, and occasionally by **venesection**. In convulsions, severe headache, or dyspnea, inhalations of **amyl nitrite** or **chloroform**, or the hypodermic injection of **morphine**,  $\frac{1}{6}$  grain (0.0108 Gm.), may be tried. When there is a probable malarial or syphilitic

origin, contracted kidney may be benefited by the use of **arsenic** and the **iodides**, respectively. Renaut reports successful results in the treatment of chronic nephritis with a maceration of young **pigs' kidneys**. The adult dose is two kidneys per day (each weighing not over 160 Gm.—5 ounces). Spillmann claims a specific effect for the internal secretion of the kidney as obtained from the venous blood of the organ.

The writer has been using **adrenalin** a considerable time, both as a diuretic and for lessening albuminuria. The majority of his patients did extremely well under it even where the ordinary methods had proved useless. I. Harris (Med. Press and Circ., June 27, 1917).

The writer reports having treated persons of 80 with uremia with 60 drops a day of the 1:1000 solution without interruption over long periods, and without the slightest inconvenience. The pulse seemed more elastic and softer while the **adrenalin** was being taken. Paoloantonio's report of its use in 30 cases of scarlatinal glomerular nephritis is cited. In children it may be given in doses of 2 or 3 drops of the solution for each year of the child's age. It can also be given subcutaneously, or by mouth, in doses of from 10 to 20 drops a day for a child between 5 and 10. Ercolani (Gaz. degli Osped. e delle Clin.; Jour. Amer. Med. Assoc., June 2, 1917).

Bright's disease is clearly amenable to **climatic treatment**. The air and soil should be warm, sunny, reasonably dry, and free from malaria and disagreeable atmospheric changes. The locality should be conducive to an out-of-door life the year round, as in southern California. The best course is to advise a warm climate first—one having moderate elevation and only a moderate rainfall, with small diurnal variations in temperature, the humidity being, perhaps, secondary in importance to temperature and wind.

Hinsdale (Urol. and Cutan. Rev., Feb., 1917).

The surgical treatment of Bright's disease, while of undoubted relief and value in relieving pain and prolonging life in some cases, should be recommended only after a careful study of each case. **Decapsulation**, an operation introduced by Edebohls, is the most important of these procedures.

Decapsulation is advised for every sufferer who has reasonable expectation of not less than a month of life without operation. The earlier in the disease the operation is performed, the better the chances for a cure. Advanced age is not a contraindication if the patient is otherwise in reasonably fair condition. Hypertrophy of the heart must be considered, and as long as the enlargement is not due to dilatation, and as long as the hypertrophy is concentric, an anesthetic may be safely used. The writer observed marked improvement in cardiac conditions in a number of patients after operation. Albuminuric retinitis is a contraindication if well marked.

The author was able to follow up 99 of the 102 patients operated on by him, an average of five years to each. Ten deaths were chargeable to the operation, although all of these were practically within a few weeks, if not days, of death by the disease. These are offset by at least 12 others in which the patients were snatched from impending death. Thirty-nine deaths occurred at periods remote from the operation, and in none of these was it a factor. Only 11 of these 39 patients were not benefited, and in the others operation did no harm; 6 of the survivors are classed as non-improved, but this is not absolutely correct, as 5 of the 6 are better in general health than before the operation. Of 11 classed as improved, the betterment has been continuous since the operation, and 3 appeared to be on the eve of restoration. The 33 cures of chronic Bright's disease from the operation would, it is

stated, justify all the work which has been done. Fourteen of the 102 patients were physicians and 5 others were members of physicians' families. G. M. Edebohls (Jour. Amer. Med. Assoc., Jan. 16, 1909).

Report of 4 cases of **Edebohls's operation** in parenchymatous nephritis in children. Of 23 cases in children in the literature, 3 were permanently cured, another was well for 2 years, then died of an acute nephritis in no way connected with the previous illness; 2 others were well as long as they were under observation; 9 others were improved. The operation may save life and result in permanent cure in acute nephritis. It may prolong life for considerable periods in chronic nephritis, and may possibly, in rare instances, result in cure. J. L. Morse (Jour. Amer. Med. Assoc., Aug. 18, 1917).

The writer recommends renal **decapsulation** in cases which fail to improve either clinically or functionally under long continued conservative treatment. It is strongly indicated in severe attacks of uremia brought on by anuria, and in these cases saves many lives; also in nephritis dolorosa and in hemorrhagic nephritis; here decapsulation of 1 kidney is sufficient; in all other cases bilateral operation is best. Karo (Münch. med. Woch., Oct. 15, 1920).

Report of the results of **renal decapsulation** in 101 cases of chronic and 18 of acute nephritis. Out of 109 operations, 47 were for "medical nephritis" and 12 of these have been permanently cured for 5 to 18 years and 8 much improved; in 10 cases the patients died with only transient relief. In 42 cases of hemorrhagic nephritis, 15 were cured or nearly cured, and 8 much improved, and 9 were cured by **nephrotomy** and 5 improved. In 2 cases the decapsulation or nephrotomy was done on the remaining kidney, years after nephrectomy; both patients have been completely cured for the 10 and 12 years to date. Gmelin (Zeit. f. urol. Chir., xiv, 247, 1924).

It is of service in cases of the parenchymatous type, where medical measures have not been successful, and in which pain in the lumbar region is a prominent symptom, thus indicating an increased tension in the cortex. It is also used in the interstitial form.

JAMES M. ANDERS,  
Philadelphia.

### BRILL'S DISEASE. See TYPHUS.

### BROMINE AND BROMIDES.

—Bromine is found in saline springs and in sea-water, but is generally obtained from the mother-liquors of salt-works. It occurs in the form of a dark reddish-brown, volatile fluid, emitting pungent and acrid fumes, caustic in action and taste. It is sparingly soluble in water (1 to 28), very soluble in chloroform, and likewise in ether and alcohol, both of which, however, it gradually decomposes. It combines freely with bases to form salts, the principal ones of which, the bromides, are extensively used.

### PREPARATIONS AND DOSE.

—The official preparations are the following:—

*Potassii bromidum* (potassium bromide), colorless, cubical, translucent, non-hygroscopic crystals, having no odor, but a bitter, pungent, saline taste. It contains about 67 per cent. of bromine and is prepared by adding bromine to a potassium solution. It is soluble in about 1.5 parts of water and in 250 parts of alcohol at 25° C. Dose 10 to 30 grains (0.65 to 2 Gm.).

The following formula provides a solution which may be used hypodermically without any ill effect and which at the same time is strong enough to furnish an ordinary dose of the salt (15 grains—1 Gm.). The formula is:—

℞ *Potassium bromide* ..... ℥ss (45 Gm.).  
*Sodium sulphate* .. ℥ss (2 Gm.).  
*Carbolic acid* ..... ℥xv (0.9 c.c.).  
*Distilled water*,  
q. s. ad ..... ℥iij (90 Gm.).

M. et ft. solutio.

Thirty minims (1.8 c.c.) of a solution prepared after the foregoing formula will contain 15 grains (1 Gm.) of potassium bromide, and this amount is directed to be injected into the front part of the thigh. If it is desired to administer 30 grains (2 Gm.) at one dose an injection of 30 minims (1.8 c.c.) is made in each thigh, rather deeply. The writer has never noticed any sharp pain follow the injection; in rare cases a slight local edema has been produced, which is easily removed by the application of ichthyol ointment. Rebizzi (*Semaine méd.*, Sept. 23, 1908).

In a study of the influence of lipoids on the solubility of haloid salts the writer found that bromides otherwise insoluble in ether become dissolved under the influence of organic lipoids or lecithin. This influence is even more pronounced with the iodides, but less so with the chlorides. Iodides are also dissolved by benzine, but not the bromides. Yoshitomi (*Acta Scholae Med. Univ. Imp., Kyoto*, Nov. 30, 1918).

Five cases of **lancinating pains** in the legs in **tubercle** were treated by Lippmann by intrathecal injections of sodium bromide in 1 per cent. solution; 10 c.c. of cerebrospinal fluid was allowed to run out and the same quantity of the bromide solution introduced. Two cases were greatly improved, 1 slightly benefited, the 4th was refractory and the 5th died of coronary sclerosis. Three cases of **spastic paralysis** of the lower limbs were similarly treated with 10 c.c. of a 1.6 per cent. solution of the bromide, which is isotonic. There was marked improvement in all. In the tabetic cases not over 3 injections were given; in the spastic cases, up to 8. The interval between injections was 14

days. In a few cases a slight reaction, disappearing in a few hours, followed an injection. Editorial (Lancet, Mar. 24, 1923).

*Sodii bromidum* (sodium bromide), a white granular powder, which abstracts moisture from the air, and has a saline, somewhat bitter, though not unpleasant, taste. It contains 77.5 per cent. of bromine and is prepared in the same manner as the potassium salt. It is soluble in 1.1 parts of water and 16 parts (vol.) of alcohol. Dose 10 to 30 grains (0.65 to 2 Gm.).

*Ammonii bromidum* (ammonium bromide), white or transparent prismatic crystals or powder having a disagreeable, pungent, saline taste. It is prepared by neutralizing hydrobromic acid with ammonia, and is soluble in 1.3 parts of water and 12 parts of alcohol. Dose 5 to 30 grains (0.33 to 2 Gm.).

*Calcii bromidum* (calcium bromide), a white, granular, very deliquescent salt having a pungent, saline taste. It contains 80 per cent. of bromine, the highest of all bromides, is prepared by dissolving calcium carbonate in hydrobromic acid, and is soluble in 0.7 parts of water and 1.3 parts (vol.) of alcohol. Dose 10 to 30 grains (0.65 to 2 Gm.).

The following preparations are no longer official:—

*Lithii bromidum*, N. F. (lithium bromide), a white, crystalline salt having a sharp, bitter taste, which deliquesces readily. It is prepared by saturating with a solution of lithium carbonate one of hydrobromic acid and is soluble in 0.6 part of water and readily in alcohol. Dose 5 to 20 grains (0.33 to 1.3 Gm.).

*Strontii bromidum*, U. S. P. IX (strontium bromide), colorless, very deliquescent crystals, having a bitter, saline taste. It contains 65 per cent.

of bromine and is prepared by neutralizing hydrobromic acid with strontium carbonate. It is soluble in 1 part of water and is very soluble in alcohol. Dose 5 to 30 grains (0.33 to 2 Gm.).

*Bromoformum*, U. S. P. IX (bromoform), a colorless and heavy liquid having a sweetish taste and ethereal odor. It is prepared by adding bromine to equal parts of caustic potash and methylic alcohol, and as used is composed of 99 parts of absolute bromoform and 1 part of absolute alcohol. It is but slightly soluble in water, but readily so in alcohol and ether, and, being readily changed by light and air, should be kept in dark, well-stoppered bottles. Dose 1 to 5 minims (0.06 to 3 c.c.).

Simple formula for bromoform and chloroform mixture:—

*Bromoform* ... 18 gr. (1.2 Gm.).  
*Chloroform* ... 8 min. (0.5 c.c.).  
*Rum* ..... 4 fl. oz. (120 c.c.).

Whereas alcoholic solutions of bromoform precipitate in an excess of water, this mixture with chloroform does not precipitate, no matter what proportions of water be present. Gay (Jour. de méd. de Bordeaux; Semaine méd., No. 11, 1900).

*Acidum hydrobromicum dilutum*, U. S. P. IX (dilute hydrobromic acid), a colorless liquid—or gas in solution—having a strong acid taste. It is a 10 per cent. solution of hydrogen bromide, and miscible in any proportion with water and alcohol. It should be kept in dark, well-stoppered bottles. Dose 20 minims to 2 fluidrams (1.25 to 8 c.c.).

**INCOMPATIBLES.**—The bromides should not be combined with strong mineral acids or given in acid mixtures, as decomposition of the bromide salt may occur. Neither

should they be combined with strong oxidizing agents such as potassium chlorate and permanganate and hydrogen peroxide. Strychnine salts are precipitated by bromides. Ammonium bromide should not be prescribed with spirit of nitrous ether.

**MODES OF ADMINISTRATION.**—Being all more or less irritating to the stomach, the bromides are best given in solution, well diluted. They are all readily soluble, both in water and in alcohol, except potassium bromide, which is soluble only in 180 parts of alcohol. They are not given hypodermically, as the injection of concentrated solutions causes local pain and irritation. They all have a bitter, salty taste. Ammonium bromide is the most unpleasant to take of the commonly used bromides, and sodium bromide the least. All the bromides except potassium and ammonium absorb moisture from the air.

**PHYSIOLOGICAL ACTION.**—The local action of bromine, especially upon the mucous membranes, is that of a very active corrosive irritant. The effects attending its internal use are best studied through the action of the various bromides, that is to say, of the *bromine ion* they contain.

**Nervous System.**—On the nervous system the bromides, in moderate therapeutic doses, act as mild depressants to the brain. In larger doses they also depress the spinal cord, especially its sensory side, and perhaps also the peripheral sensory nerve-endings. In the brain the effect is particularly marked on the intellectual centers and the psychomotor areas. Mental activity is reduced; external objects and movements are perceived, but fail to excite any in-

terest. The mind is thus in an apathetic state predisposing to sleep, which, if surrounding conditions be favorable, finally results. The sleep is not very deep, however, and is often not refreshing, the patient feeling dull and heavy for some hours after awakening. The effect on the psychomotor centers has been demonstrated in dogs. Upon exposure of the brain, the application to these areas of an electrical stimulus which would ordinarily cause epileptiform convulsions produces only localized muscular contraction after bromides.

It is characteristic of the effect of bromides on the central nervous system that the communications between the various sensory cells and centers are interfered with by bromide, so that in any reflex action, either in the brain or cord, the response to stimulation is strictly limited and localized. This is exactly opposite to the effect of strychnine, which exaggerates the reflex effects of a stimulus by facilitating its passage to distant sensory nerve centers.

In the spinal cord and the centers of the cranial nerves, full doses of bromides decrease reflex excitability. Nausea is no longer felt when the throat is touched, no winking occurs on touching the conjunctiva after very large doses, while the reflexes of the genital organs are notably reduced. With very large doses, too, general sensation is also diminished, the skin becoming more or less anesthetic, owing to depression both of the sensory centers and nerve-endings. The medullary centers are but little affected by bromides. In the frog the effect of bromides on the spinal cord is much more marked than on the brain. Reflex activity may be



entirely lost at a time when voluntary movements are still made.

Experiments on animals in which serious symptoms were produced by the administration of bromides. The animals developed ataxia progressing to fatal paresis. These symptoms, ordinarily regarded as bromide poisoning, are due to chlorine deficiency and it was possible to save the animals by injecting **sodium chloride**. They recuperated entirely in twenty-four hours with no sign of their previous serious condition. The continuous administration of the bromides causes a considerable retention of bromine ions in the blood. Consequently sodium chloride is excreted in order to prevent the concentration of salts in the blood. The deficiency of the chloride leads to serious consequences, which may be relieved by the injection of **normal saline solution**. In the treatment of epileptics this action is obtained by administering bromides and simultaneously reducing the salt in the food. Wyss (Med. Klin., Bd. xlvii, S. 1749, 1908).

Experiments described by the writers showed that the bromide ions exert a stimulating effect on the respiratory center. Hooker and Macht (Jour. Pharm. and Exper. Therap., Feb., 1918).

**Circulation.**—No perceptible effect is produced when the bromides are taken by the mouth, even in large doses. Hydrobromic acid injected in animals causes a slight but temporary rise of blood-pressure which has been ascribed to a direct action on the vessel walls, followed, with very large doses, by cardiac depression. Potassium bromide, injected intravenously, tends to depress the heart, but this is because of the potassium rather than the bromide ion.

On the *respiration* bromides cause a slight depression with full doses, breathing becoming slower. The *temperature* is lowered by very large

doses, probably owing to lessened movement. As to *metabolism*, the output of phosphorus-containing compounds in the urine is sometimes decreased, probably owing to lessened nervous activity.

*Locally* the bromides are mildly irritating. Beside causing salivation and thirst, large amounts irritate the stomach, producing nausea, vomiting, and occasionally diarrhea.

**Absorption and Elimination.**—The bromides are rapidly absorbed, but very slowly excreted. After a single dose, the urine has been found to contain bromide for as long as two months (more often twenty days). The bromine ion, circulating in the blood, appears to be readily accepted by the tissues as a substitute for a portion of the chlorine ion normally present in them as chlorides, and this probably accounts for the slowness of its elimination. Administration of bromides is followed by increased output of chlorides in the urine, indicating that the former partly replace the latter in the tissues. When bromides are taken continuously, they accumulate in the body. The amount excreted daily increases progressively, however, until, after a certain time, generally in two or three weeks, the amount eliminated in the twenty-four hours equals that taken in, a state of equilibrium being established. A large quantity of bromide is then present in the body, especially in the blood, brain, and kidneys. The acid of the gastric juice then consists partly of hydrobromic acid. The effects of such an accumulation of bromides in the body are those of a single dose in an exaggerated form, and, when especially marked, constitute the condition known as "brom-

ism," to be described later. In addition to passing out in the urine, the bromides are eliminated also through the alimentary tract, slightly through the skin, and, in nursing women, slightly with the milk.

As to the *physiological action of metallic ions in bromides*, they differ considerably:—

*Sodium* is indifferent or neutral as to action. The amount of it present normally in the body is so large that the addition of a small amount is without effect. The action of sodium bromide is thus practically that of the bromide ion.

*Potassium* is a depressant to the whole central nervous system and, less markedly, to all muscles, including the heart. The nerve-depressant effect of the bromide in potassium bromide is considerably strengthened by it. The circulatory depressant effect of potassium is hardly noticeable, however, when potassium bromide is taken internally, except on prolonged use; marked depression is seen only when it is injected intravenously in animals. Potassium bromide is a little more irritating locally than sodium bromide.

*Ammonium compounds*, when injected hypodermically or intravenously, act as a pronounced stimulant to the spinal cord, medullary centers, and heart-muscle, but when taken by the mouth much of this stimulating effect is lost. The effect of the bromine in ammonium bromide is but little modified by it except with large doses. On the brain ammonium does not act as a stimulant; if anything it assists the action of the bromine on this structure. Ammonium bromide, like the potassium salt, is more irritating locally than sodium bromide.

*Strontium*, i.e., its ion, is but very slightly absorbed from the alimentary canal; hence it has no effect when taken internally, and the only way in which it modifies the action of the bromine in strontium bromide is to delay slightly its absorption into the system, since the salt has to be decomposed before the bromine is absorbed. Strontium is said to be, with calcium bromide, the least irritating of all the bromides.

*Calcium* may be said to have the same effect as strontium; it remains practically unabsorbed, and slows the action of the corresponding bromide.

*Lithium* depresses the nervous system and circulation almost like potassium when given intravenously, but in addition it has a special tendency to cause gastrointestinal disturbances on prolonged use. It is readily absorbed.

*Zinc* (zinc bromide formerly official) acts as an astringent and irritant.

The last three of these salts, as well as dilute hydrobromic acid, are seldom used in therapeutics.

Bromides, given in a single dose or in 2 doses given near together, are retained for quite a time in the organism. In subjects with normal kidneys the largest amounts of the bromine are eliminated during the first 3 days, after which the remainder is eliminated in decreasing amounts. On the thirty-fifth day the quantity eliminated represents only 72 per cent. of the bromine absorbed. The elimination during the first 24 hours was only 3.2 per cent. of the total amount ingested. In subjects with nephritis the elimination was 3 times less during the first 10 days than in subjects with a normal urinary function. W. Authenrieth (Münch. med. Woch., July 9, 1918).

**BROMIDE POISONING.**—Fatal acute poisoning with bromides is al-

most unknown in man. Enormous single doses produce such symptoms as gastrointestinal pain, nausea and vomiting, thirst, headache, circulatory weakness, low temperature, loss of reflexes, anesthesia of the skin, and especially marked drowsiness, lasting for several days, with slow return to normal as the drug is gradually eliminated.

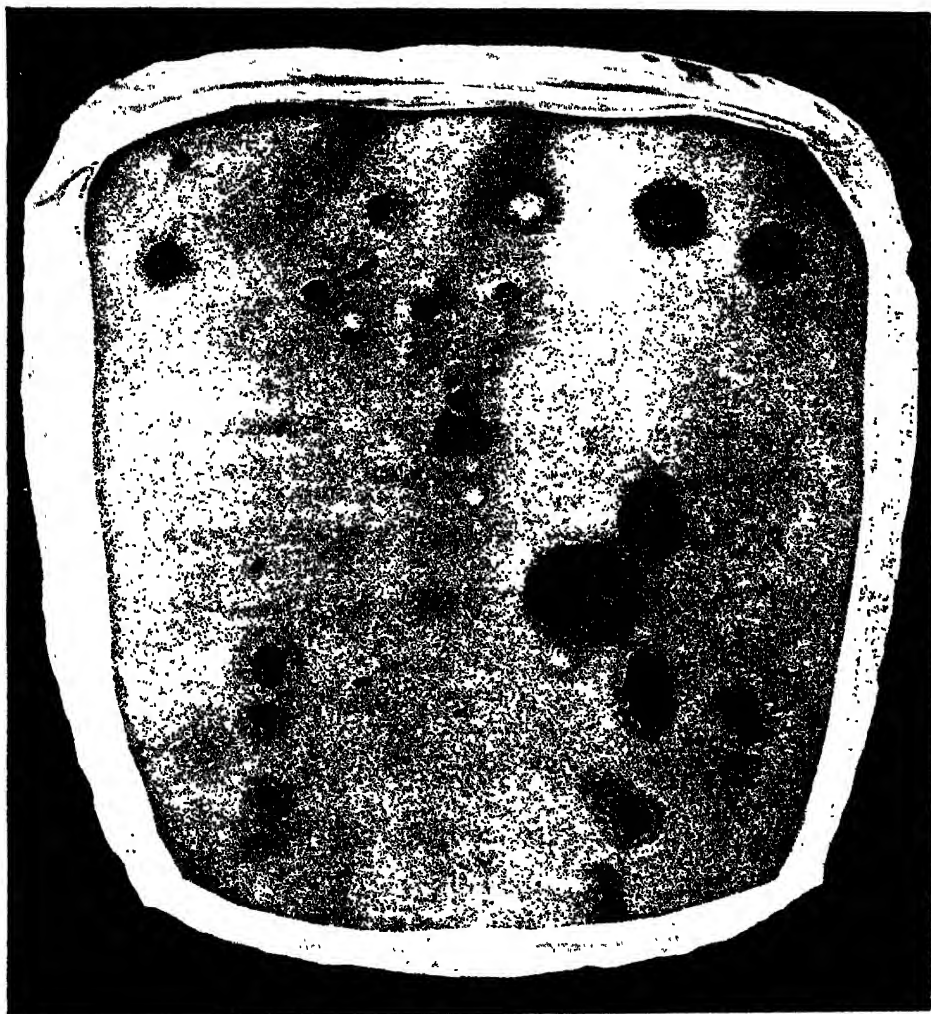
Two cases of bromoform poisoning; the children found lying side by side, with breath smelling strongly of bromoform, with faces pale, eyes closed, pupils contracted, and limbs flaccid. Artificial respiration, brandy, and strychnine hypodermically administered, and lavage with hot water and hot coffee brought consciousness in about one and one-half hours. Stokes (Brit. Med. Jour., May 26, 1900).

Case of bromoform poisoning in a child 16 months old. The points of especial interest were: The rapidity with which unconsciousness came on, and the corresponding rapidity with which the child returned to consciousness, after a period of over four hours; the pinpoint pupils, which might have led to an incorrect diagnosis of opium poisoning. The bromoform administered to the child was not the last in the bottle, and therefore concentrated, as 6 fluidrams (24 c.c.) remained in the ounce bottle, after the second dose. H. K. Dillard, Jr. (Ther. Gaz., April, 1903).

Case of poisoning by bromide of potassium in a woman aged 35 years who was nearly nine months pregnant. She was of a neurotic temperament, but otherwise perfectly healthy. She had suffered from facial neuralgia and was ordered one evening a 6-ounce (180 Gm.) mixture containing 30 grains (2 Gm.) of bromide of potassium in the ounce (30 Gm.). This she placed under her pillow and helped herself to at short intervals during the night. It was afterward found that she had a private store of the drug which she also took, so that

she swallowed altogether about  $4\frac{1}{2}$  drams (18 Gm.) of the salt in less than twelve hours. When seen on the following day she was in a very drowsy and semicomatose condition. She could be aroused by speaking loudly to her and answered—apparently without understanding the question—in a hesitating and tremulous manner, but was unable to express herself intelligently on account of aphasia. This was extremely well marked, and but for the history and the absence of other symptoms would have strongly suggested a cerebral lesion. Thus the medicine was referred to as soup, pastry, as cushion, and so on. She seemed conscious that she was using the wrong word and after several repetitions of it would relapse into silence. Left to herself she passed at once into a semicomatose state. The respirations were deep, regular, and slightly stertorous, but not slower than normal. The pupils were normal in size and reacted well to light and to accommodation. The pulse was 76, quite regular, and of good volume and tension. The fetal heart could be heard quite plainly. The knee-jerks were exaggerated and although the muscular movements were slow and feeble the patient was able to leave her bed without assistance and totter about the room. There was no anesthesia of the skin or mucous membranes and she took food readily and with apparent appetite. These conditions continued without any change for two days. On the third day the aphasia had begun to disappear and by the end of the fourth day the patient was practically well. She had no recollection of what had happened during the first two days. No treatment was adopted except the administration of 5-minim (0.3 c.c.) doses of liquor strychnine every four hours. Three weeks afterward the patient gave birth to a vigorous male infant, the labor being rapid and uneventful.

The case is instructive on account of the well-marked aphasia and the fact that labor and the fetus were



Bromide of Potassium Eruption.

(Atlas de l'Hôpital St. Louis.)



quite unaffected by the drug. The aphasia is difficult to account for. A. C. Stark (*Lancet*, May 2, 1908).

**BROMISM or CHRONIC BROMINE POISONING** results from continuous use of bromides in large doses. The liability to it varies in different persons, the old or emaciated subjects being especially susceptible to it. In some cases it appears suddenly after several months of bromide treatment without ill effects. The symptoms are numerous. Prominent among them is a skin eruption, generally of the acne or pustular type, and sometimes quite severe, due to the excretion of the bromide through the skin. In children this may assume the form of small, brownish-red elevations of the skin which are rather characteristic. Ormsby has reported three cases of bromide eruption which were mistaken for blastomycosis. Lesions tend to occur at points of previous inflammation, *e.g.*, vaccination scars, injuries, etc.

Case of bromide eruption resembling a serpiginous syphilide. The lesions showed a healing center with atrophic scarring, a scabby border, and many superficial ulcers beneath the scabs. The patient had taken bromides for eighteen months, and 9 different diagnoses had been made, and salvarsan administered. Withdrawal of bromides was followed by healing, and resumption six months later led to recurrence. Eruptions seen in other bromide cases were macular, papular, pustular, scaling, papilliform, warty, and fungating, with dark brown pigmentation. J. B. Shelmire (*Texas State Jour. of Med.*, Sept., 1921).

Case of burn, in an epileptic woman taking potassium bromide, which refused to heal until the bromide was discontinued and luminal substituted. S. Pulvirenti (*Policlinico*, Oct. 24, 1921).

Bromide eruption in a nursing infant of 6 months. The mother, who

was receiving 45 grains of sodium bromide a day, did not develop any eruption. The eruption in the child appeared 4½ weeks after the beginning of bromide medication. F. H. Boone (*Can. Med. Assoc. Jour.*, Aug., 1922).

Intravenous injections of 250 to 500 c.c. (½ to 1 pint) of decinormal sodium chloride solution at intervals of 2 to 3 days yielded marked benefit in 3 women with mental and cutaneous manifestations of bromism. In 1 case acute nephritis and shock symptoms were observed. The nephritis promptly cleared up when the bromide disappeared from the urine. U. J. Wile (*Arch. of Derm. and Syph.*, Sept., 1923).

Case of bromide eruption due to addiction to bromo-seltzer in a man aged 40. The amount taken daily contained 25 to 126 grains of bromide, 10 to 54 grains of acetanilid and 3 to 14 grains of caffeine. The papulo-pustular eruption appeared in a few weeks, in addition to the bluish pallor of acetanilid intoxication and nervousness. The rash disappeared about 1 month after cessation of use of bromo-seltzer. J. F. Waugh (*Jour. Amer. Med. Assoc.*, May 17, 1924).

There is also an increase of bronchial and nasal secretions, an unpleasant odor of the breath, and similar taste, all believed to be due, at least partly, to liberation of bromine through decomposition of the bromides by body acids. Digestive disturbances due to local irritation by the drug are also complained of, the appetite being lost. There may also be gastric pain. Mental and nervous phenomena also occur; they include pronounced failure of memory, depression of spirits, general indifference, and defective speech, drowsiness, partial insensibility of the skin and mucous membranes, diminished reflexes, and unsteady gait. The facial expression is stupid, and a

marked degree of imbecility is sometimes reached. In advanced cases the respiration is slowed, the temperature lowered, and even the power of voluntary motion and speech is practically lost. Death occasionally results, oftener from infectious disease such as pneumonia, to which the depressed state of the patient predisposes him, than from the direct action of the drug.

**TREATMENT OF BROMINE POISONING.**—Stopping the drug is soon followed by cessation of the symptoms. The skin eruption due to bromides can often be prevented by giving arsenic along with them, using 1 or 2 minims (0.06 or 0.12 c.c.) of Fowler's solution to each dose of bromides. Strict cleanliness of the skin and occasional purgation are also desirable.

**THERAPEUTICS.**—The bromides are used mainly for their calmative effects in **general nervousness** and **insomnia**. In moderate degrees of **nervous excitement** and excessive irritability brought on by overwork, grief, or worry, and in **insomnia** due to excitement, bromides are useful as mild depressants, though less certain than chloral hydrate or trional, the bromides not being true hypnotics, but merely favoring sleep by lessening the response to external stimulation. Again, the slowness of their elimination is apt to induce rather prolonged general depression. In **insomnia** due to pain the bromides are of little or no value, except in certain cases of headache, but they enhance the action of morphine, which may be given simultaneously in small doses to alleviate suffering while inducing sleep. Sodium bromide is slightly less irritating to the stomach than the

potassium salt, while acting less powerfully. A mixture of the sodium and ammonium bromides is specially recommended by some:—

℞ *Sodii bromidi*,  
*Ammonii bromidi* ...āā živ (16 Gm.).  
*Aqua* ..... fžj (30 c.c.).  
*Elixir aromatici*...q. s ad fžiii (90 c.c.).

M. Sig.: Teaspoonful in water before retiring.

The dose of bromide used ranges from 10 grains to 1 dram (0.65 to 4 Gm.); generally 20 to 30 grains (1.3 to 2 Gm.). Peppermint, wintergreen, or preparations containing citric acid are among the best flavoring agents for bromides. Syrups only make the taste more unpleasant.

In **epilepsy** the bromides are used considerably, but often unwisely. In 85 to 90 per cent. of cases the continuous use of bromides will cause diminution in the frequency and violence of the epileptic attacks. In some instances the attacks are entirely removed as long as the drug is used, but return when it is stopped, while in a very small proportion of cases a cure is said to be obtained. They should not be deemed curative, but useful to suppress fits while curative measures are used (Spratling). The bromides act by lowering the excitability of the cortical motor centers which are subject to periods of abnormal irritability—a period now known to represent an effort to rid the blood of spasmogenic toxics.

When pushed in epilepsy, bromide of potassium produces apathy, listlessness, a total lack of interest in surroundings, a dull, sodden facial expression, and if carried still further a mental condition not unlike bromide poisoning. Toxic doses arrest the heart in diastole; the long-continued use of the drug results in a weakened and irritable condition of the heart

and a general impairment of the circulation. W. P. Spratling (Ther. Gaz., June, 1903).

The bromides are being increasingly used in **melancholia** and similar conditions. Exact estimation of the degree of brominization is important. When much salt is taken, the bromide has comparatively little action. The relative bromine and chlorine content of the body can be determined by a single blood analysis. In severe **epilepsy**, enough bromides must be given to bring the relative bromine content of the blood up to 20, 25, or even 30 per cent. In the urine the corresponding relative content would be from 15 to 25 per cent. The diet must be salt-poor, reduced to from 5 to 15 Gm. ( $1\frac{1}{4}$  to  $3\frac{3}{4}$  drams) salt per day. To obtain a 15, 20, 25 or 30 per cent. relative bromine content of the urine, when the patient is getting 5 Gm. ( $1\frac{1}{4}$  drams) of sodium chloride a day, the sodium bromide dose should be, respectively, 1.6, 2.2, 3 and 3.8 Gm. (25, 33, 45 and 60 grains). If potassium bromide is used instead of sodium bromide, the dose should be increased by 15 per cent. It is the combination of chloride and bromide that is effectual, neither alone, and only their proper combination. Bernoulli (Corresp. Bl. f. schweizer Aerzte, Aug. 11, 1917).

Warning that unusual irritability, mental confusion, or violence in a patient taking bromides is a signal for a decrease in the dosage. The author ascribes the irritability of temper of long-standing epileptics partly to the constant, excessive use of bromides. Toxic and exhaustion cases react unfavorably to these salts, and mental cases as well as alcoholics are unusually susceptible to bromide intoxication. In some cases of chronic heart disease, bromides not only depress and enfeeble the heart action but, if long continued, induce mental symptoms. E. L. Hunt (N. Y. State Jour. of Med., July, 1921).

A. S. Priddy (Therap. Gaz., Oct., 1924), writing from the State Colony for epilep-

tics and feeble-minded in Virginia, asserts that most of the chronic epileptics admitted to the institution are found to be temporarily suffering as much from chronic bromism as from the disease itself. The practice of giving bromides indiscriminately and freely increases the difficulty of treating these patients. The cumulative effect of their prolonged use contributes to the development of dementia; the immediate effects are mental depression and stupidity. O. S. Hubbard (*Ibid.*) has observed a few instances of acute mania apparently due to the use of bromide. One patient in particular on several occasions became violently excited under sodium bromide. E. A. Strecker (*Ibid.*) has seen periods of mild excitement with a large element of confusion and an indefinite hallucinosis, seemingly due to bromides.

As stated by Hubbard (*loc. cit.*), epileptic patients who have taken much bromide should have the drug reduced slowly to avoid status epilepticus. At the same time some other sedative may be substituted. Tonics, particularly **strychnine**, seem to help the stomach and circulation. Much attention should be given to the stomach and bowels, and frequent **warm baths** administered.

The full depressing action is not obtained from a single large dose, but only by keeping the body saturated with the drug by means of moderate daily doses, such as 15 to 20 grains (1 to 1.3 Gm.) morning and evening. In obstinate cases the dosage is progressively increased until the convulsive attacks are brought under control or symptoms of chronic intoxication appear. Potassium bromide is the most efficient single bromide, though a mixture of several salts, *e.g.*, potassium and ammonium, or potassium, sodium, and ammonium bromides, is preferred by many. By greatly decreasing the amount of sodium chloride in the diet of epileptics, it is found that the daily dose of bromide required to saturate the system with it can be lessened, the tissues taking up the



bromide all the more readily owing to their lack of sodium chloride.

In **chorea** and **hysterical spasms** bromides are also useful, though not of special importance, as in epilepsy. In **delirium tremens** and other forms of delirium they may be used to assist the action of the stronger hypnotics.

As spinal and medullary depressants the bromides are extensively used. In **spinal convulsions**, **tetanus**, and **strychnine poisoning** and other convulsive disorders, bromides are given in large doses to depress the sensory spinal centers, but large doses, such as 2 to 4 drams (8 to 16 Gm.), are necessary to obtain the spinal effect in these cases. If combined with chloral, which depresses the motor side of the cord, a maximum degree of spinal depression is obtained. Ammonium bromide should be avoided in these conditions, as the ammonium in large doses is a spinal stimulant.

In **nervous conditions** related to the **genital organs**, including the reflex nervous symptoms succeeding upon the **menopause** and in **uterine disorders**, also in the case of **excessive seminal losses** in the male, bromides are of value as spinal sedatives.

In other reflex disturbances, such as **whooping-cough** and **vomiting of pregnancy** or **seasickness**, bromides are also useful, preventing sensory irritation from causing motor response.

In affections with severe **itching** which is not controlled by local applications, bromides may also be used to depress the sensory centers and nerve-endings.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

## BRONCHITIS, ACUTE AND CHRONIC, and their Various Forms and Complications.

**DEFINITION.**—Bronchitis is an inflammation of the mucosa of the bronchial tubes. **Acute** bronchitis is caused most frequently by infection. It may be caused by toxic matter conveyed by the circulation, or by the inhalation of liquid or solid matter in a finely divided state, or by irritating gases. Acute bronchitis is most often a diffuse process involving the larger divisions of the bronchi and the trachea.

**Chronic** bronchitis is usually dependent for its chronicity on some condition, other than simple infection, which interferes with the circulation or drainage of the bronchial tract or has caused permanent damage to the bronchial structure.

## ACUTE INFECTIOUS BRONCHITIS.

The term "cold" is commonly used to designate an acute infection of the upper respiratory tract and this condition frequently is accompanied by a *tracheobronchitis*. When colds are prevalent in a community the outbreak may assume the proportions of a mild epidemic, and in this case there is apt to be a marked similarity in the symptoms shown by the affected individuals, and in the tendency of these individuals to develop complications.

**SYMPTOMS.**—Bronchitis is caused by so many infectious agents that it is impossible to draw a clear picture of its symptoms or course. In general, the onset is acute, but a "cold" with conjunctivitis, rhinitis and pharyngitis with all the constitutional symptoms of an acute infection may have existed for some time before any signs of bronchitis or tracheitis are evident. The de-

gree of toxemia and constitutional symptoms depends on the nature of the infection and the degree of involvement. Extensive involvement limited to the trachea and large bronchi causes much cough and expectoration, but as a rule comparatively little toxemia, whereas extensive involvement of the smaller divisions may cause profound toxemia, the so-called capillary bronchitis being practically a bronchopneumonia.

The view that bronchitis is merely a secondary disease, infection traveling down from the nose, throat, sinuses, tonsils or teeth, is being carried too far. All the pathogenic flora of the upper air passages are common in warm, dry climates, but bronchitis is rare. A chill due to exposure is an undoubted etiologic factor, but more particularly if the atmosphere is moist as well as cold. When the vital resistance is lowered, and especially during sleep, when the controlling influence of the nervous system is partially suspended, one is much more liable to the catarrhal effects of cold. In a cold, damp climate many aged persons contract a fatal bronchitis in bed. The writer has seen a bronchitic patient, with edema of the lungs and the so-called death rattle in his throat, rescued from death by rapidly raising the temperature of his bedroom with a blazing fire. Sir James Barr (*Med. Jour. and Rec.*, Apr. 16, 1924).

Bronchitis may come on abruptly, with no premonitory signs, but commonly, as already implied, it is preceded by or accompanied with signs of infection in the upper respiratory tract. These signs consist of dryness of the membranes of the mouth and nose, soreness of the throat, coryza, and hoarseness and cough due to laryngitis. Acute bronchitis caused by the commoner infecting organisms is accompanied by the constitutional symptoms of acute infection, chilliness followed by a fever of slight de-

gree, and malaise. There is usually a sense of tightness or soreness in the chest or substernal region, and an irritative cough.

On examination, the temperature will be found to be moderately elevated, the pulse slightly accelerated, a troublesome cough will be noted, and the signs of inflammation of the bronchial mucosa will be evident on examination of the chest. In the first stages, dry râles and harsh breath sounds will be found, followed shortly by large moist râles widely distributed throughout the chest. The percussion note is apt to be hyperresonant.

In an ordinary mild bronchitis the condition may clear up rapidly, the temperature returning to normal and the discomfort rapidly abating as the cough becomes "looser" and loses its irritative quality. Coughing yields free mucoid or muco-purulent expectoration, and seems to be provoked only by the presence of secretion in the respiratory passages. Cough now ceases to be distressing or painful. The cough and expectoration gradually diminish, and in a few days have disappeared and convalescence is complete.

The above represents the ordinary course of a mild infection of the larger bronchi in a robust or resistant individual. Diffuse involvement of the bronchioles is a different matter, and is frequently of serious moment. It is frequently seen in young children and in the aged, and may often be a most grave condition. The onset is sudden. The symptoms are those of a profound infection and toxemia. The serious nature of the attack is reflected in the effects on both respiration and circulation. While the

presence of secretion in the large bronchi causes large noisy râles, it does not seriously obstruct breathing, but widespread inflammation in the bronchioles seriously interferes with the passage of air to or from the pulmonary vesicles and materially hampers respiratory function. As a rule an infectious bronchiolitis or capillary bronchitis soon becomes a *bronchopneumonia* (*q.v.*), and must be considered and treated as such.

At times the surface tension of the tissue cells becomes lowered, thus permitting germs to break through the barrier, become intracellular, and induce disease. Some Gram-negative microbes, indeed, are believed capable *per se* of lowering the surface tension. Either because of atmospheric conditions or infection, germs other than those of which the persons are carriers may fix themselves on the nasorespiratory mucous membrane and induce a type of catarrh peculiarly their own, which then descends into the bronchi.

An unusual type of bronchitis in an elderly man is reported, featured by low temperature without signs of physical depression and a gelatinous sputum, at times dislodged with much difficulty and pain. The accumulated sputa appeared as a clear, yellow jelly, as if stained with picric acid. This color was found due to *Sarcina flava*. Pneumococci were also present, perhaps accounting for the jelly-like sputum. In the stage of decline there were attacks of dyspnea due apparently to bronchospasm, though no evidences of asthma were present. Sir Thomas Oliver (*Brit. Med. Jour.*, May 3, 1924).

**DIAGNOSIS.**—A simple acute bronchitis can be differentiated from the bronchitis of measles or German measles only by observing the development of other symptoms and signs of these diseases. When bronchitis develops in connection with

severe coryza, lachrymation and conjunctivitis in an individual who has not had *measles*, this disease must be suspected, as the bronchitis of measles may be active for three or four days before any rash develops. Koplik's spots may be evident.

*German measles* shows reddening of the palpebral conjunctiva, and coryza, with enlarged glands in the post-cervical region, along the lower edge of the scalp posteriorly, and most characteristically over the mastoid processes. The post-auricular glands will be felt for 3 or 4 days before the rash appears.

*Pertussis* starts as a tracheitis and bronchitis of the larger tubes. The duration of the disease, with paroxysms of cough becoming characteristic after a couple of weeks, will indicate the nature of the infection. Diagnosis by identification of the Bordet-Gengou organism is not generally applicable.

*Typhoid fever* may show an acute bronchitis at its onset. The course of the temperature and the increasing degree of prostration should soon indicate that something more than a simple bronchitis is in question. *Paratyphoid fevers* may cause a severe bronchitis, indeed, even a bronchopneumonia, the pulmonary and bronchial involvement being sufficiently severe to account apparently for the fever and prostration of the patient. If the course of disease is prolonged and the appearance of the patient suggests typhoid, an agglutination test with the patient's serum against strains of the typhoid group may show a positive Widal reaction developing about 10 days or more after the onset of the illness. The paratyphoid organisms can be recovered from the sputum in culture in these cases of paratyphoid bronchitis.

In all cases of recurrent acute bronchitis the possibility of *tuberculosis* must be kept in mind. In subjects with tuberculosis of the genital organs, ischio-rectal abscess or bone tuberculosis, the onset of a general miliary infection must be considered. Secondary *syphilis* may be first indicated by an acute bronchitis, followed promptly, however, by skin and mouth lesions which will show the nature of the trouble possibly before a positive Wassermann can be obtained.

### CHRONIC BRONCHITIS.

Bronchitis may become subacute or chronic. If an ordinary infective bronchitis persists, it is necessary to search carefully for some complicating factor.

If there is no destruction of the mucosa, the bronchitis should clear up rapidly. If symptoms do not clear up, it may be because destruction of the cells of the mucous layer has taken place, or deeper damage has occurred, tending toward bronchiectasis. Tissue repair may not proceed normally in the presence of a chronic infection, and the presence of lues or of tuberculosis in the body may be the cause of an acute bronchitis persisting in chronic form. Pulmonary tuberculosis of the fibroid type, through its effects on the lungs and bronchial structures, may be the cause, apart from the constitutional effects of the infection. Emphysema is a very common cause after middle age in general, and particularly in the subjects of anthracosis (miners, grinders, pot-terers, etc.). Cardiac disease is a frequent cause of delay in the clearing up of symptoms after an acute bronchitis. Diabetes and chronic renal disease are often underlying factors in the production of chronic bronchitis,

and gout may cause an acute as well as a chronic bronchitis.

An ordinary acute infection may become chronic through an individual lack of resistance to the infecting organism or through some condition, as diabetes, favoring the persistence of infection by lowering resistance. The late stages of wasting diseases and senility favor the persistence of such infection.

**SYMPTOMS.**—The symptoms of chronic bronchitis, as those of acute bronchitis, depend to a great extent on the nature of the infecting organism. The constitutional effects may be mild and unnoticed, or they may be severe, particularly in the aged. Cough and mucoid or purulent expectoration are constant accompaniments of this condition. The presence of diffuse coarse râles can always be detected. It should be remembered that the bronchial mucosa has great power for quick repair of the damage sustained through mild infections, and if a chronic bronchitis is present it is usually an indication that some factor other than infection is active. It may again be emphasized that simple chronic bronchitis is a rare condition.

In the early stages of chronic bronchitis, no constant X-ray picture is found, the commonest change, however, being an accentuation of the normal lung markings, particularly of the smaller bronchial divisions, usually to a different degree on the 2 sides, sometimes with small areas of relative opacity in the surrounding parenchyma, denser than the fluffy areas of early tuberculous infiltration. Physical signs of hilus gland enlargement are frequent, but not always confirmed by the X-ray. Probably chronic bronchitis, peri-bronchitis and pneumonitis are present in varying degree in different cases which are clinically much the same. In a study of 26 such cases, the

writer found a rather even distribution of the incidence by decades from 5 to 65 years. The onset was insidious in 15, and followed an acute illness in 11. Five had no foci of infection; 13 had infected tonsils; 12, nasal sinus infection; 9, apical dental infections, and 6, infections in the appendix, prostate, gall-bladder or middle ear. The treatment comprised general **hygienic measures** to enhance resistance, **removal of foci of infection**, and **auto-genous vaccines**. C. N. Meader (Ill. Med. Jour., Sept., 1924).

**ETIOLOGY AND PATHOLOGY.**—Chronic bronchitis has been classified in various ways, *e.g.*—

1. Simple bronchitis following acute infectious bronchitis.

2. Chronic bronchitis occurring in constitutional diseases, such as Bright's disease, gout, etc.

3. Chronic bronchitis due to pneumokoniosis.

4. Chronic bronchitis dependent on infection of the upper respiratory tract, as sinus and tonsil infections.

5. Chronic bronchitis due to myocardial and valvular disease.

6. Chronic bronchitis occurring in chronic lung disease, as tuberculosis, emphysema, etc.

Warren reviewed 120 cases, of which 34 were classed by him as simple or primary bronchitis and 86 were secondary. Other series have shown an even larger proportion of secondary cases.

Special forms of bronchitis are described as **dry**, **purulent** and **putrid**. These conditions, while described at length by various authors, do not represent specific conditions of infection or of pathological changes. In most cases of chronic bronchitis the discharge becomes purulent sooner or later, and a putrid bronchitis may result from various infections and conditions.

**Plastic or fibrinous bronchitis** presents a more definite picture. In this condition casts of portions of the bronchial tree are formed by a characteristic exudate, which may loosen and be coughed up.

Fibrinous bronchitis would be found less rare if the sputa of patients were more carefully examined. The diagnosis is made only by finding long, branching bronchial casts in the sputum of patients who do not have tuberculosis, diphtheria, pneumonia, nor any other primary bronchial disease. The cause of the condition is unknown. I. C. Walker (Amer. Jour. Med. Sci., June, 1920).

Chronic bronchitis classified as *primary*, including bronchitis due to irritants such as cotton, flour or other dust, and gouty bronchitis, and *secondary*, including cases secondary to an infection in the upper respiratory tract, cases following some acute pulmonary infection, and bronchitis following gasping in ex-service men. There are also many cases of wrong diagnosis, in which the symptoms are due either to a weak heart with congestion or edema, bronchiectasis, or interstitial pneumonitis. J. B. Hawes, 2d (Boston Med. and Surg. Jour., Aug. 2, 1923).

Chronic bronchitis of *nasal origin* emphasized. The persistent cough is usually accompanied by more or less obstruction to nasal breathing—"the bronchitis of the corked nose." These patients virtually blow their nose into the pharynx, infecting the lymphatics of the latter, as well as the larynx and trachea. The most frequent sources of infection in the author's cases were, in order: Chronic purulent ethmoiditis, adenoids, maxillary sinusitis, chronic purulent sinusitis, and pan-sinusitis. He recognizes 3 types of cases: (1) Infection spreading equally through the main branches of the bronchi and to the alveoli, sometimes with dilatation of the bronchioles and physical signs of emphysema, cough increased in damp, cold weather and by lying down, with hawking, coughing and sometimes profuse expectoration on

arising. (2) Tracheal or phlegmonous type, with severe, painful paroxysms not unlike asthma, followed by moderate expectoration, the cough being accompanied by substernal pain. (3) Localized form, with involvement of the lungs in patches, at times only a small spot, frequently near the apex; clearing up of the physical signs after brief local and general treatment assists in the differentiation from tuberculosis; the writer's cases of this type showed maxillary sinus infection. W. F. von Zelinski (Med. Jour. and Rec., Feb. 6, 1924).

Bronchitis resulting from "**epidemic influenza**" has been extremely common since the epidemic of 1918, and these epidemic cases are probably duplicated in sporadic form. Many individuals are encountered who have had an active bronchitis for several years following an attack of influenza. These are frequently cases of bronchiectasis, usually multiple, or of multiple abscesses, or of encysted and partially drained empyema.

Separate consideration given to a *subacute* form of *bronchitis*. The patient is usually seen after about 3 weeks of illness, beginning with a bad cold or mild influenza. Severe cough followed, worse at night and after exposure to cold, damp air, and usually dry, slightly productive and paroxysmal. Weakness and erratic appetite are complained of, and a history of night sweats and an occasional streak of blood in the sputum may be elicited. Physical examination is usually negative except for numerous sibilant and mucous râles over both lungs, often widely disseminated but most often confined to the bases. The pulse and temperature are generally normal. The X-ray is negative or may show some small areas of mottling. Differentiation from tuberculosis is best made by the history; the normal expansion, equal on the 2 sides; the multiplicity of râles anteriorly and posteriorly over both lungs; absence

of crepitant râles after expiration and cough, and sputum and X-ray studies.

Treatment consists of avoidance of night air, though **fresh air** and **sunlight** are beneficial; possibly **rest in bed** for 2 weeks; restriction of pastries, pork meats and tobacco; general tonics, such as the **elixir of iron, quinine and strychnine**, and if feasible, 6 weeks in a warm climate, such as Florida. The patient should be impressed with the fact that he does not have "consumption"—a fear usually foremost in his mind. P. Davis (Va. Med. Mthly., June, 1924).

The influenza of the 1918 epidemic was carefully studied in many localities. Different observers were impressed by different phases of the condition. Descriptions vary considerably as regards the course of complications and pathological changes. Even the etiological agent is still a matter of dispute. There was certainly a common cause underlying all of these epidemic cases. Probably the majority of qualified observers considered the influenza bacillus (Pfeiffer's bacillus) to be the causative agent. Yet it is believed by many that a filtrable virus is the underlying cause, or a combination of such virus with some other organism or organisms, particularly the influenza bacillus. There was a wide difference in the disease picture in different localities, both as regards the so-called influenza and the development of complications.

The type of bronchitis, the tendency to pneumonia, the type and severity of pneumonia, and the tendency to pulmonary abscess, bronchiectasis, and empyema varied according to the prevalent complicating infections; thus, while the epidemic cases occurring at the same time in a given locality would follow the same trend in the symptomatology, course and tendency to complication, cases in another locality might show

an entirely different series of complicating infections and consequently a very different disease-picture as regards the course of complications and prognosis.

In order to understand the reasons for the persistent cough and bronchitis remaining in these complicated influenza cases, it is necessary to consider briefly the pathological changes induced during the disease. Grosh and the writer studied the disease at Camp Hancock, Ga., and had an opportunity to observe closely large groups of cases showing few complications and also other groups complicated by severe *Streptococcus hemolyticus* infection. The laboratory studies included excellent bacteriological work and about 150 necropsies on selected cases. We observed 7 cases of tracheo-bronchitis giving a pure culture of *Streptococcus hemolyticus* with 4 deaths occurring before the influenza epidemic.

[There was in these cases an intense peri-bronchitis. On sectioning the lung, the dense round-cell infiltration about the bronchioles made the cut ends stand out like solid plugs thickly studding the lung surface. In 3 cases no pneumonia was demonstrable, although in the last to succumb the infection had extended into the alveoli in considerable areas. There was diffuse ulcerative bronchitis involving virtually the whole bronchial tract. It appeared to begin in the trachea and larger tubes and gradually extend into all the subdivisions, penetrating the walls and setting up a reaction which induced a dense zone of round-cell infiltration about each bronchus and bronchiole. This pathological picture was repeated with great regularity as a complication in the influenza-pneumonia cases during the later period when hemolytic streptococci were prevalent complicating organisms in the epidemic cases.—ROBERT G. TORREY].

Another type of involvement was observed and has frequently been de-

scribed as due to the influenza bacillus. The inflammation is diffuse in the bronchial tract, extends deeply into or through the mucosa and often produces bronchiectasis. Great numbers of the smaller bronchi may be dilated, particularly toward the base of the lungs. Especially early in the epidemic, large groups of individuals might suffer from "influenza" with little sign of complicating bronchitis, but with a fairly high incidence of pneumonia of a mild type. Thus, our first 102 cases of this group of pneumonias were not complicated by the streptococcus infection and showed only 4 deaths, while the first group of pneumonia cases complicated by the *Streptococcus hemolyticus* infection showed a mortality of nearly 50 per cent. and a high incidence of empyema in those recovering. The pneumonia cases were apt to show pneumococcus in the lung cultures and in some of the blood cultures. A high incidence of influenza bacillus was noted in the throat smears and sputum studies, but some groups showed a very low percentage of positive culture for influenza bacillus early in the epidemic. These cultures were made by the same workers and by the same technic as were the cultures of the other groups showing a very high incidence at the same time. At other camps or in other cities, the prevalent complicating organisms were different; thus, at Camp Benjamin Harrison, according to the reports received from the base hospital, the common complicating infection was a *Streptococcus pyogenes aureus*, producing multiple lung abscesses.

Our conception of the course of the disease was that the primary lesion was an attack upon the integrity of the alveolar wall. This

was common to all cases and was shown at the onset. In the absence of bronchitis and severe cough, recovery was apt to be prompt and uncomplicated. Severe cough damaged the lung and favored pulmonary infection and acute emphysema. Bronchial damage was sustained particularly through infection by hemolytic streptococci and influenza bacilli; pulmonary consolidations of the massive type, through pneumococcic infection, and pulmonary abscess, by a variety of organisms, particularly the streptococci.

Observation of the bronchi and lungs of the patients succumbing to the disease indicates that the damage to the bronchial mucosa and to its supporting structures in a severe case of influenza is such that the recovery of function will be delayed and incomplete, bronchial drainage being interfered with, infectious material retained with resulting irritation and reinfection, and a state of chronic bronchitis favored. Many patients suffering from severe infection and profound lung and bronchial damage as shown by symptoms, signs and X-ray studies cleared up in a remarkable and almost unbelievable manner, but we are still called upon to see great numbers of individuals who have suffered from chronic bronchitis since an attack of epidemic influenza, and in many of these the persistence of infection may well depend on bronchial damage. There is no specific infectious agent in these cases. The infectious organisms may change from time to time, one growth supplanting another, but the conditions favoring infection and preventing drainage remain. These conditions are dilatation or sacculatation of the bronchi, denudation of the bronchial mucosa by removal of the layer of ciliated epithelium,

stricture of the lumen by fibrosis, rigidity of the wall, abnormal irritability with spasm (asthma), general or local. There must be great power for repair in the bronchial mucosa, but a combination of the above factors of damage will defeat the efforts toward repair unless in some way adequate drainage of the contents of the bronchi can be maintained.

The symptoms of cough, expectoration, sometimes hemoptysis, recurrent febrile attacks and toxic symptoms lead to a suspicion of tuberculosis. The signs of pulmonary infiltration and fibrosis further this suspicion. Tuberculosis can be ruled out only by repeated negative findings in a large number of sputum examinations carried on from time to time.

**Bronchitic asthma** or **diffuse bronchiolar spasm** may be due to toxic causes acting through the nervous system from a distant source of toxin, or may depend on infection of the bronchial tract, which is rendered hypersensitive and responds by spasm on slight provocation. Whether the provoking action is local or whether the action takes place through central effect is not clear. It may be that the infection of the bronchi furnishes enough toxic matter to act as does a focal infection elsewhere in the body. It is probable, however, that much of the action is local, as it is a common experience to find signs of bronchiolar spasm persistent in an area surrounding a focus of chronic infection, as a lung abscess or infected bronchiectatic or tuberculous cavity. There is seldom found a condition of chronic infectious bronchitis which depends on the virulence of the infecting agent for the continuance of the infection. A bronchitic asthma may continue the infection through bronchio-



lar spasm preventing drainage and through ciliary destruction; bronchiectasis may continue the infection by providing an undrained collection of infected material with damage of the contiguous mucosa; or, an acute ulcerative bronchitis due to infection or to a chemical agent, as irritant gas, may result in a denudation of the bronchial surface or ciliary destruction. It is probable that chronic sinus infection may cause repeated reinfections of the bronchial tract, producing what is practically a chronic bronchitis.

Case of chronic bronchitis with asthmatic attacks of 5 years' standing. The woman was forced to be in bed most of the time. Marked temporary improvement followed 2 attacks of febrile influenza. The author conceived the idea, therefore, of inducing fever with **autogenous mixed vaccines**. Like benefit resulted, and had been maintained for 3 months. Hagens (Ugeskr. f. Laeger, Dec. 31, 1925).

The tracheal and bronchial structure is similar. There is a lining membrane consisting of specialized columnar epithelial cells bearing large numbers of actively motile cilia, a fibro-elastic layer, involuntary muscle fiber, cartilage, and an outer fibrous coat. The mucosa and muscle are both of great importance, as disturbed conditions of either may interfere with bronchial function. Normally the surface of the bronchial mucosa is moist, and the collecting mucus is swept upward toward the trachea by constant waving of the epithelial cilia. This action of the cilia tends to spread the mucus droplets, forming a thin film and favoring constant evaporation. Interference with the ciliary activity causes collections of mucus, and when large areas of bronchial wall are denuded, the normal upward current of surface flow must, of course, cease altogether, with

collections of mucus below this area until forcible expiration or cough expels it. It is readily seen that retention of moisture in any area favors infection and that the septic material may cause irritation of the mucosal cells with which it comes in contact. Irritation of the mucosal cells causes increased production of mucus, with aggravation of the trouble.

A large number of cases of chronic tracheo-bronchitis with asthma have been studied in the bronchoscopic clinics maintained by Chevalier Jackson's groups, and the reports from these clinics have added greatly to our knowledge of the behavior of the lungs and bronchi under various conditions of disease. After exhaustive studies of the material obtained from the bronchi in these cases by aspiration and swallowing, Moffitt has made some interesting and important observations. He states:—

"The bronchial columnar epithelial cells are 40 to 50 micra in length. There are as many as 480 cilia attached to a cell. The ciliary movements are at the rate of 6 per second. There is a secondary ciliary movement which forces secretion and foreign particles from the wall into the lumen. The cilia are 18 to 20 micra in length. A basal root process connects the cells of the uppermost layer to the basement membrane. In the asthmatic subject the following changes may be observed in these cells: Relative or complete loss of ciliary motion, actual loss of cilia, fatty degeneration of the cells."

His observations lead him to believe that the replacement of the cilia lost by disease does take place, or that if the cell is destroyed it is promptly exfoliated and its place as-

sumed by a non-ciliated cell from a lower layer which may then acquire cilia. Bronchoscopic observations as well as autopsies indicate that deep ulceration going below the epithelial layer does not occur in asthma.

The above statements are based on Moffitt's observations.

The writer has observed a case in which autopsy revealed apparently active regeneration of the epithelium in the trachea and main bronchus where there had been a smooth apparently fibrous surface presented to the bronchoscope a few months before, this condition resulting from gas necrosis. The epithelium was apparently spreading from numerous islets and making good progress toward covering the surface.

**Gas Bronchitis.**—While many cases of chronic bronchitis seen of late have been those having their origin in epidemic influenza, one frequently encounters patients who have suffered from the effects of gas exposure during the World War. Figures attributed to the Surgeon-General's Office gave the number of gas casualties receiving treatment abroad at over 76,000, with deaths of about 1100; consequently, there were probably about 75,000 men listed in overseas hospitals as gas casualties who returned to this country. Many of these were of negligible severity and caused no permanent effects. Many were cases of burns from mustard gas with no bronchial effects, but many other cases seen here show undoubted results of gas bronchitis in men who never applied for a hospital treatment in Europe.

*Mustard "gas"* is not a gas at ordinary temperature, but as delivered from explosive shells was encountered as a spray of fine droplets which on in-

halation settled in the upper respiratory passages and the bronchi. *Chlorine* is extremely irritating on inhalation, causing choking, coughing, and sneezing, and does not penetrate freely into the lung vesicles because of the bronchial spasm immediately set up by its irritation. Both of these gases cause a severe ulcerative bronchitis with marked tissue destruction.

*Phosgene* is not irritating in admixture with air, and can be breathed unnoticed. It thus enters the lung vesicles without obstruction. It is easily absorbed by the moist tissues and on entering the tissues becomes extremely destructive. Being non-irritating at first, it penetrates deeply, and thus rapidly causes necrosis about the areas where it is absorbed in sufficient concentration. It sets up a very active and destructive bronchitis, and also has an immediate destructive effect on the walls of the lung alveoli.

The symptoms of chlorine and mustard gas poisoning are those of extremely active severe bronchitis. The symptoms of phosgene poisoning include symptoms of pulmonary edema with extreme anoxemia. These gas cases, particularly those of the phosgene group, are apt to show nervous and circulatory symptoms which have been designated variously as "N. C. A." and "D. A. H." (neuro-circulatory asthenia and disordered action of the heart). These cases are apt to show a chronic bronchitis, but in many of them the circulatory and nervous symptoms are too pronounced to be attributable to the bronchitis. The patients appear ill, apprehensive and worried about themselves. They are apt to look like subjects of tuberculosis. A patient showing a chronic

bronchitis with a history of exposure to irritant gas will often present a characteristic picture. The resemblance to a subject of pulmonary tuberculosis is very striking and the differentiation difficult.

Dyspnea on exertion, rapid breathing on slight effort, precordial pain on exertion, undue fatigue, cold and cyanotic hands, loss of weight, poor chest expansion, cough, expectoration, hemoptysis,—these are frequently found as the signs and symptoms elicited in gas cases. Examination indicates the existence of chronic bronchitis, pulmonary fibrosis and emphysema of varying degree. The circulatory and respiratory disorder is particularly marked in the subjects of phosgene poisoning, and in this group pulmonary fibrosis and emphysema may also be particularly marked.

As has been said, it is extremely difficult to differentiate this condition from pulmonary tuberculosis, and repeated examinations of the sputum must be made to satisfy the observer on this point.

The writer has had an opportunity to study a large number (about 300) of these cases in a fairly recent stage, and later observed many of these patients a few years after gas exposure, and has been impressed with the continuing importance of the condition.

Case of a man who had been gassed and later suffered from bronchitis and attacks of unconsciousness following cough. These attacks ceased under treatment with *belladonna*. A. Sézary (Bull. Soc. méd. des hôp. de Paris, Apr. 13, 1923).

*Ammonia* may be inhaled accidentally through mishaps to the machinery of cold storage plants or refrigerating apparatus, and in sufficient concentration can cause a very severe and de-

structive bronchitis which seems to be progressive in the severity of its symptoms, leading to diffuse chronic bronchitis and emphysema.

**Bronchitis Due to Constitutional Diseases.**—Apart from infections, the toxic manifestations of certain constitutional diseases may result in troublesome chronic bronchitis.

*Gout* causes a characteristic irritation of the bronchial tract, and *nephritis* with retention of nitrogenous toxic bodies will produce a bronchitis which is very persistent. Other diseases, as *rickets* and *diabetes*, may show similar manifestations.

A very definite bronchitis may be seen in the *hypothyroid state* which is promptly cleared up by **thyroid** therapy.

*Secondary syphilis* characteristically shows a bronchitis which, if untreated, may persist long enough to be thought to be a chronic condition. Examination in such a case should reveal the true nature of the condition in showing secondary lesions of the skin and oral mucosa, sore throat and enlarged glands. *Tertiary syphilis* may show a bronchitis and tracheitis which is apparently of specific nature and diffuse in its distribution. This condition is not unusual. Gumma of the bronchus has been reported; likewise ulceration and cicatricial stenosis resulting from ulcer, these conditions being probably infrequent.

Three cases of syphilis of the trachea and bronchi. The Wassermann reaction was positive in all. One recovered under **specific treatment** and the other 2 presented typical lesions at the autopsy; in 1 of the latter the diagnosis of bronchial syphilis had been made before death. The writer concludes that while the *symptoms* of this condition are rather variable, the characteristic ones are those of obstruction, *viz.*, a peculiar type of dyspnea,

with labored, prolonged inspiration and shorter, easier expiration; paroxysms of excessive dyspnea, sufficient to cause syncope or even death; cough, usually hard, brassy and paroxysmal; stridulous sounds, particularly during inspiration; frequently an inspiratory sinking-in of the tissues of the root of the neck, epigastrium and lower intercostal spaces; more or less profuse sputum, and a limitation in the mobility of the larynx. Stimson (*Amer. Jour. Med. Sci.*, May, 1921).

The most important connection between syphilis and chronic bronchitis is found where there exists a stubborn chronic infective bronchitis in a subject of tertiary or latent syphilis. It is a well established fact that in the presence of syphilis tissue repair is not normal and resistance to local infection may be below par. Acute local infections tend to become chronic and slight infections by ordinary organisms which would otherwise be of a trivial nature become troublesome through their persistence. This tendency is well known in the tissues of the respiratory tract, and the bronchi and trachea show the tendency to chronic inflammation as do the larynx and paranasal sinuses.

**Focal Infection of the Teeth and Sinuses.**—Focal infection of the teeth and sinuses may maintain a chronic bronchitis. Whether this is accomplished through repeated reinfections or through toxic irritations is not clear, but a persistent chronic bronchitis will often clear up promptly when such localized infections are eradicated.

**Pulmonary Tuberculosis.**—The association of chronic bronchitis with pulmonary tuberculosis is obvious. The tuberculous pulmonary changes produce bronchial disturbance by pressure or traction, by circulatory changes,

by the favoring of mixed infections, and by the discharge of irritating products of infection and decomposition from tuberculous cavities. This phase of the question is so obvious as to require no discussion, but what must be emphasized is that every case of chronic bronchitis must be looked upon as a possible case of pulmonary tuberculosis. Examination of the sputum for tubercle bacilli is a simple procedure and one that should be employed much more frequently than is the case.

The following test recommended to differentiate tuberculosis and bronchitis: To 5 c.c. of a 24-hour specimen of sputum add 20 c.c. of normal saline and 5 or 6 drops of acetic acid. Shake thoroughly and filter. Test the filtrate by boiling or with nitric acid for albumin. In 57 cases of chronic bronchitis this albumin test was invariably negative. In 98 per cent. of 42 cases of proved tuberculosis, the test was positive at some period during the disease. Cornell (*Bull. Can. Army Med. Corps*, June, 1918).

Attention called to the risk to other persons attending unrecognized pulmonary tuberculosis in old people, which frequently assumes the form of a chronic bronchitis without any marked impairment of general health. Numerous cases of tuberculosis in children may be traced to their grandparents, whose sputum unexpectedly contains tubercle bacilli. Whenever, in asthma in old persons, no nasopharyngeal nor cardiorenal cause for the condition can be found, repeated examinations of the sputum for tubercle bacilli should be made. A. Pissavy (*La médecine*, May, 1921).

Bronchitis apparently caused by a *spirochete* has been described by Castellani and reported since by many observers. The disease was found to occur in epidemic form in the tropics and showed a characteristic picture.

Isolated cases are frequently encountered by clinicians in the temperate zone in which bronchial or pulmonary disease of acute or chronic course yields sputum that on examination shows spirochetæ resembling the organism of Vincent, probably associated with a fusiform bacillus. These cases are frequently supposed to represent instances of infection of the bronchial or pulmonary tissues by a specific pathogenic organism with the production of bronchitis or pneumonia. More information is needed before these cases can be properly viewed. The organisms of Vincent can be found with such frequency in any necrotic lesion of the mouth that there seems doubt as to their pathogenicity. Epidemics of Vincent's angina occur usually in institutions where dietary conditions are such as to favor oral necrotic conditions (such as scurvy), or in troops living largely on canned or preserved foods (trench mouth). These organisms can be found swarming in the mouth, lesions of scurvy, in necrotic areas in diseased tonsils, and in dead tissue about the edges of the gums, and the writer feels that it is not at all unlikely that necrotic tissue in the lungs or bronchi might be similarly invaded with these organisms, playing purely a saprophytic part.

[The writer once observed a patient, apparently very ill, who showed signs of pulmonary disturbance in the mid-portion of the right lung, interpreted as consolidation. There was copious expectoration of a gelatinous consistency which showed a tangled mass of spirochetæ and fusiform bacilli in incredible numbers. During one night the patient filled a pint cup with sputum of this character. Recovery was prompt and apparently complete. There was no specific treatment other than large quantities of orange juice and small doses of potassium chlorate.—ROBERT G. TORREY.]

The rôle played by these organisms has not yet been made clear, although it seems that Castellani's cases were probably distinct from the sporadic cases frequently reported in Europe and America.

Report of 2 cases of *ulcerative, pseudomembranous bronchitis due to Vincent's organisms*, in which the bronchial lesions were observed bronchoscopically.

The first of these cases had failed to recover after Vincent's angina, developing fever and a cough, with offensive, occasionally blood-streaked sputum. Lung expansion was somewhat limited, with a great variety of râles. Bronchoscopy showed both bronchi affected. Much secretion was aspirated and applications of 20 per cent. silver nitrate were made at 6 later bronchoscopies, complete recovery following. In the second case an abscess of the lung had been suspected, but bronchoscopy showed the left bronchus occluded by whitish material which came away with forceps in several casts, leaving ulcerated surfaces. Much foul pus was aspirated. The casts showed predominance of Vincent's organisms. The patient went to sea without further treatment, and later stated his cough and expectoration had ceased in about a month. Vincent's infection should be excluded in every case of ulcerative or membranous bronchitis or chronic lung suppuration. Chevalier Jackson (Jour. Amer. Med. Assoc., Dec. 6, 1924).

Other organisms have been noted as causing chronic bronchitis, *e.g.*, **Bacillus paratyphosus**, among English and French troops during the World War. These organisms have been noted as the cause of pneumonia or bronchitis in connection with paratyphoid fever, and also as the apparent cause of a chronic bronchitis when a history of the acute febrile attack was lacking. **Friedländer's bacillus** causes peculiar lung changes resem-

bling tuberculosis, which may cause the persistence of a bronchitis.

An amebic form of bronchitis described. The writer has been struck by the favorable effects of *emetine* in overcoming certain cases of atypical bronchitis, some of which had a history of dysentery. Hemoptysis occurred in these cases, and the sputum was viscid and mucoid, and showed amebæ and amebic cysts. The condition occurs independently of any pulmonary or hepatic abscess. In the patients who did not have a history of dysentery the stools were always negative for amebæ. Under *emetine* treatment, preferably intravenous, the amebæ gradually disappear from the sputum. Petzetakis (Bull. Soc. méd. des hôp. de Paris, Aug. 3 and Nov. 8, 1923).

**Plastic or Fibrinous Bronchitis; Pseudomembranous or Croupous Bronchitis.**—Pseudomembranous or croupous bronchitis is characterized by the presence in more or less extensive portions of the bronchial tree of casts of the bronchi and bronchioles, consisting of tenacious mucoid and fibrinous material, which are expelled during paroxysms of cough. These casts are white, grayish or pinkish in color, and can be floated out in water, showing main trunks and multiple branches and twigs which conform to the structure of portions of the bronchial system.

This condition may occur as an acute process, or may be a chronic bronchitis with repeated attacks or paroxysms in which casts are formed and expelled. These paroxysms are marked by a rise in temperature and pulse rate, and symptoms of oppression in breathing or sense of suffocation. There may be chest pain and "tight" cough with increasing dyspnea. As the cough loosens casts may be expelled. These are of varying size and

may be small and recognizable only if floated out in water, or may represent bronchi of considerable size.

Examination of the chest during an attack shows the signs of an intense and diffuse bronchitis with involvement of the small tubes, the signs resembling those of an attack of asthma with râles throughout the chest and with portions of the lung showing almost no pulmonary function. The casts are said to develop more toward the bases of the lungs. The temperature increase is usually of moderate degree, but instances of high temperature have been recorded.

There is no constant bacteriological finding in this exudate, and the cellular content of the casts has no regularity. There is usually a moderate leukocytosis during attacks, and cases showing marked eosinophilia are reported. A well-marked tendency toward association with cardiac disease and with pulmonary tuberculosis has been observed and reported by several writers.

The diagnosis of fibrinous bronchitis rests on the recognition of bronchial casts. Their presence may be expected when there are recurrent asthmatoïd or suffocative attacks of brief duration and sputa of a firm consistency are coughed up as the attack progresses. Examination of the sputa in water may in such cases show them to be bronchial casts.

Fibrinous bronchitis has not been shown to be a specific disease. There are probably different types of bronchial involvement which might under certain conditions yield a plastic instead of a mucoid or purulent exudate as ordinarily seen in bronchitis. The association of fibrinous bronchitis with tuberculosis indicates the need for complete study in a case

where bronchial casts are found. Some of the cases reported show a strong resemblance to asthma in the mode of onset of the recurrent attacks and in the blood picture and the cell content of the exudate.

**Pneumokoniosis.** — Exposure to dusts of various kinds over long periods of time produces a type of pulmonary fibrosis seen in miners, grinders, potters, workers in wool waste, millers, stone cutters, etc. The picture varies somewhat according to the type of irritant, whether organic or inorganic and chemically active or inert. The chief effect is pulmonary, but there is present also a chronic bronchitis.

In the late stages of the disease the bronchial condition is that seen with advanced pulmonary fibrosis and emphysema due to any cause, and bronchiectasis is of frequent occurrence. In certain occupations, as brass grinding or working with bronzing powders, an extremely active and destructive chronic bronchitis may be set up and maintained apart from the secondary results of pulmonary fibrosis.

**Bronchitis Due to Foreign Bodies.** — Chronic bronchitis resulting from the presence of a foreign body lodged in a bronchus has been shown by Chevalier Jackson and his associates to be an important condition.

Vegetable foreign bodies, including peanuts and melon seeds, cause a prompt tracheobronchitis with toxemia, cough and fever; the effects are more severe in young children. Bone and shell cause all the symptoms of chronic abscess or bronchiectasis. Non-obstructive metallic foreign bodies may cause few symptoms or signs for weeks or months; obstructive bodies cause atelectasis, wet lung and abscess.

The chief physical signs, according to Jackson and McCrae, are those of partial or complete bronchial obstruction, decreased expansion, fremitus and breath sounds distal to the obstructions, and emphysema or wet lung. Fluoroscopy shows a flattened diaphragm, diminished excursion, and obstructive emphysema on the affected side.

Foreign body must be suspected where there are indications of bronchiectasis, pulmonary abscess, unilateral bronchial spasm or signs suggesting basal tuberculosis. An X-ray study should be made in these cases.

Treatment demands the services of a skilled bronchoscopist.

**TREATMENT. — Simple Acute Bronchitis.** — Most cases of acute bronchitis are the result of acute infection of the respiratory tract, and the whole of the respiratory tract must be considered in the treatment. It is certain that inflammation and infection can be favored by irritation of the bronchial tract as a result of inhalation of noxious substances. It is probable that these factors can be favored by fatigue and chilling of the body. It is also probable that overeating and constipation may produce this result by causing a toxemia. Excessive amounts of alcoholic drinks will cause bronchitis and favor infection.

The *prophylactic measures* to be observed, particularly where an infection of the upper respiratory tract is already established, include the avoidance of all the above conditions. If a person has "caught cold" it is well to start treatment at once by a **saline cathartic**. This may be of little service if the condition is solely due to infection, but as a toxemia is frequently a factor it is probably advisable in most cases

to begin treatment by a rapidly acting purge and have the patient drink **freely of water**. **Magnesium sulphate** is a satisfactory saline cathartic, or a mixture of the **sulphates of magnesium and sodium** may be used. From  $\frac{1}{2}$  to 2 ounces (15 to 60 Gm.) of magnesium sulphate should be sufficient. A **purgative water** such as Hunyadi or Pluto serves the purpose very well.

It is well to restrict the **diet** at the onset of a cold for a brief period of time, particularly if there be any marked degree of fever, and the **water intake** should be **increased**. If toxemia be an important factor in the case, **sweating** is probably of value, and the combination of purgation, sweating and increased water intake may clear up the condition. Where infection is the main factor the value of sweating is questionable.

**Rest** is of unquestionable value in the infection cases. It is always safe to put the patient to bed at least for a day or two, but unfortunately it is not always possible. If the fever be high, the pulse-rate markedly accelerated, or if the patient appears really ill, this course should be insisted upon. It may be that the nose will become more obstructed in the recumbent position, which may favor congestion of the nasal mucosa; in this event extra pillows should be used so that the head and shoulders are raised.

In a simple acute infection of the upper respiratory tract, recovery should be prompt unless infection persists actively in the tonsils or the accessory nasal sinuses. If infection of the frontal, maxillary, ethmoid and sphenoid cells continues, bronchitis is apt to follow and to be recurrent. To avoid the development of bron-

chitis one must try to prevent the occurrence or persistence of sinus infection. Congestion and swelling of the nasal mucosa may be diminished by raising the head upon the extra pillows, as suggested; blockage of the sinuses may likewise sometimes be relieved in this way.

Instillation into the nose of some non-irritating organic silver compound may be of great service. The bactericidal power under these conditions may be questionable, but the effect on the tissues of the nose seems as a rule to be good. If this application causes irritation its use should be at once discontinued. The writer is familiar with the preparations known as **argyrol**, **silvol**, and **arkase**. Some such preparation may be used, a few drops in each nostril 3 or 4 times daily. Small doses of **atropine** or **belladonna** frequently repeated are very useful in reducing congestion of the nasal mucosa and preventing sinus blockage with persistent infection. The patient may be directed to dissolve a tablet of atropine sulphate,  $\frac{1}{100}$  grain (0.00065 Gm.), in from 5 to 10 spoonfuls of water, and take a spoonful every 10 or 15 minutes if the nose seems congested. This often seems more efficacious than the taking of larger doses infrequently.

Atropine or belladonna may be combined with other drugs and taken at the beginning of the attack. A favorite combination is:

℞ *Ext. belladonna*, gr.  $\frac{1}{10}$  (0.0065 Gm.).  
*Caffeina citrata*, gr. j (0.65 Gm.).  
*Acetphenetidini*, . gr. ij (0.13 Gm.).  
*Acid. acetylsalic.*, gr. iij (0.2 Gm.).

Ft. in caps. No. j.

One such capsule is to be taken every hour for 4 or 5 doses. **Dover's powder** in divided doses up to a total of 5 to 10



grains (0.3 to 0.6 Gm.) is a favorite remedy, and may be combined with the above capsule to advantage.

It is well to avoid extremes of heat or cold. An overheated and stuffy room favors congestion of the nasal mucosa, and extreme cold or rapid changes of temperature probably have the same effect.

As to further prophylactic measures against the development of a bronchitis, it is probable that **creosote** is of value. This drug is said to be eliminated through the bronchial mucosa; it is apparently not only non-irritating to the bronchial tract, but seems to have a soothing effect in bronchitis, and may well appear in the bronchial mucus in sufficient concentration to exert some inhibitory influence on certain infections. The drug has an unpleasant taste and a strong odor. It may upset the stomach and disturb digestion. It may be administered well diluted in water or milk, or in the form of tablets of a combination of calcium and creosote, which are widely used and seem to be well tolerated if milk or food be taken at the same time. A commonly used tablet of this description is sold under the trade name of **calcreose**, and purports to contain equal parts by weight of creosote and a calcium salt in a 4 grain (0.26 Gm.) coated tablet. Two such tablets may be used 2 or 3 times daily by most patients without gastric discomfort if taken with milk or other food. **Guaiacol carbonate** has been used in place of creosote for the same purpose, but is said to be distinctly depressing, and seems to be less used now than formerly.

With the onset of bronchitis there is apt to be an increase in the temperature and other signs of infection,

with some soreness in the chest, cough, difficulty in breathing and scanty expectoration. The patient's comfort may be enhanced by an alkaline draught, *e.g.*, **potassium citrate**, 10 grains (0.6 Gm.) in a half glass of water every 2 hours. An expectorant such as **ammonium carbonate** may be given. If the cough is very "tight" small doses of **iodide** may be added and are very efficacious, rendering the mucous secretions less viscid and making the cough looser.

Many cases of acute bronchitis could be aborted or cut short by prompt, energetic treatment. A person with a severe chill followed by distress in breathing should have a **warm mustard bath**, be put to bed in a warm room, and if he still feels chilly, have a glass of **hot punch** or some **hot gruel**. No food should be given for 24 hours, but plenty of **hot water** allowed. Reid's panacea of **Dover's powder** with **acetylsalicylic acid** and **acetphenetid**in may be given. Next morning a **saline purge** should be taken, and the patient then remain in bed for 2 or 3 days on a starvation diet. In cases where the lungs have become waterlogged, the sympathetic is insufficiently active and the vagus overactive; hence, **atropine**,  $\frac{1}{60}$  grain (0.0012 Gm.), and **adrenalin** solution, 5 to 10 minims (0.3 to 0.6 c.c.), should be given **intravenously** every 2 hours until the danger is past. As free calcium ions in the blood are practically always deficient, soluble **calcium hypophosphite**, 2 or 3 grains (0.13 to 0.2 Gm.), should be added to each injection, and a liberal supply given by the mouth. The atmosphere should be **warm**—about 70° F.—and as **dry** as possible, large amounts of dried calcium chloride or strong sulphuric acid being placed in soup plates about the room. There is no need for food, and the quantity of fluid should only be sufficient to moisten the lips and mouth. Sir James Barr (*Med. Jour. and Rec.*, Apr. 16, 1924).

The question of checking the cough by an **opiate** must always receive careful consideration before such a dose is advised. If the cough is not severe and serves to clear the tubes of large amounts of mucus, it is probably unwise to check it. If, on the other hand, the cough is hard, dry and irritating, and due largely to laryngeal or tracheal irritation, it is probably doing harm rather than good; it is distressing to the patient, accomplishing little of advantage, and may be doing much damage through strain of the lung vesicles and forcing of infective material into the smaller bronchial divisions. Such a cough may be relieved by one of the many popular prescriptions containing **ammonium chloride, iodide, Brown's mixture, ipecac, squill, terpin hydrate, apomorphine**, or other drug enjoying repute as an "expectorant."

The most certain and satisfactory method of relieving the cough, however, is by some form of opium or one of the narcotic derivatives. **Codeine** in doses of  $\frac{1}{16}$  to  $\frac{1}{2}$  grain (0.004 to 0.03 Gm.) may suffice, but it is unreliable. **Heroine** seems the most satisfactory agent in many respects; a dose of from  $\frac{1}{48}$  to  $\frac{1}{6}$  grain (0.0013 to 0.004 Gm.) in a syrup or elixir, *e.g.*, the **elixir of terpin hydrate**, is a popular combination and one exceedingly satisfactory in allaying an irritative cough. **Morphine, tincture of opium or paregoric** in small doses may be used. **Morphine sulphate**,  $\frac{1}{24}$  to  $\frac{1}{2}$  grain (0.0025 to 0.005 Gm.); 3 to 5 minims (0.18 to 0.3 c.c.) of the tincture of opium, or a teaspoonful of paregoric may be given to an adult, alone or in combination with some elixir or some other expectorant to allay the cough.

There is probably no danger of

starting a drug habit by treating an acute bronchitis with a limited number of small doses of an opiate. It is unwise, however, to give opium to any one who has ever been an addict except in case of dire necessity. Opium when given to children must be administered in very small doses. Paregoric is the safest form for administering to children, as there is less chance for serious error in prescribing and dispensing this dilute and bulky preparation than is the case with the more potent ones.

In acute bronchitis, **rest in bed**, together with **diaphoresis** and **hot moist applications**, is indicated. The air in the room should be **warm and moist**, but no irritant inhalations of turpentine, etc., should be employed. **Sedative drugs** may be given for severe cough, and **mucilaginous preparations** administered when the fluidity of the secretion is to be increased. If capillary bronchitis develops, **mustard packs** or **mustard baths** are advisable. Preliminary to the patient's first venture into the open air, which should be delayed until complete recovery of the mucous membranes has occurred, **cold rubs** should be administered, and upon leaving the house the mouth should be kept closed and the precaution taken of walking slowly. Goldscheider (Deut. med. Woch., Sept. 15 and 22, 1922).

If there is much bronchial spasm, **atropine** is useful. The dose required for temporary relief of bronchial spasm varies in different individuals. As little as  $\frac{1}{500}$  grain (0.00013 Gm.) may be an effective dose, and as much as  $\frac{1}{50}$  grain (0.0013 Gm.) may be tolerated without discomfort. Atropine is seldom required for the acute bronchitis, but is very useful in the chronic cases of bronchitic asthma and in the rhinitis of the early stage of a "cold," and may be necessary for sinus blockage co-incident with acute bronchitis.

In the ordinary case of acute bronchitis the use of an opiate may be omitted unless the cough becomes distressing. In influenzal bronchitis it is of great importance to reduce the cough during the early stages as the cough is very severe, and pronounced lung damage is directly due to the hard coughing.

[A useful procedure to increase the fluidity of discharges and facilitate their expulsion, according to Davis, is the giving of water copiously and preferably hot. Serviceable liquefying expectorants are sodium bicarbonate and the citrate and acetate of potassium and of ammonium. In children breathing is made much easier by enveloping of the chest in hot poultices of flaxseed or similar material. Hot tub baths at regular intervals may be substituted. In fatigue the result of rapid and difficult breathing, strychnine in full doses may be desirable to secure better emptying of the bronchi. Oxygen inhalation will often greatly lessen cyanosis and subjective distress, when present. Some cases of subacute capillary bronchitis are allied to rheumatism and are benefited by salicylates. Internal use of ichthyol, 5 grains (0.3 Gm.) 3 times daily, has been recommended in subacute cases attended with profuse expectoration.

The following formulæ have been found useful:—

℞ *Guaiacolis carbon-*  
*atis* ..... 0.3 Gm. (5 grs.).  
*Codeinæ*,  
*Aloini* .....āā 0.015 Gm. (¼ gr.).  
*Strych. sulphatis* ... 0.001 Gm. (⅙₄ gr.).

For one capsule.

Take 1 three or four times daily.

℞ *Ammonii chloridi* . 10 Gm. (2½ drs.).  
*Morphinæ sulphatis* 0.2 Gm. (3 grs.).  
*Antim. et pot. tar-*  
*tratis* ..... 0.1 Gm. (1½ grs.).  
*Fl. ext. cascar.*  
*sagrad.* ..... 20 c.c. (5 drs.).  
*Syr. yerba santa*,  
 q. s. ad ..... 120 c.c. (4 oz.).

Take 1 teaspoonful in water three or four times daily.

℞ *Ammonii carbo-*  
*natis* ..... 0.3 Gm. (5 grs.).  
*Codcinæ*,  
*Aloini* .....āā 0.02 Gm. (⅓ gr.).

For one capsule.

Take 1 four times daily.

℞ *Tinct. sanguinariae* 10 c.c. (2½ drs.).  
*Tinct. opii camph.*,  
*Syr. scillæ comp.*,  
 of each ..... 40 c.c. (10 drs.).  
*Syr. tolu.* ..... 120 c.c. (4 oz.).

Take 1 teaspoonful in water four to six times daily.

According to Kerley, a diet containing an excess of fats and carbohydrates sometimes causes recurrent bronchitis in children, which is relieved by cutting down the carbohydrates.—Ed.]

In acute bronchitis in children, the writer applies treatment as for bronchopneumonia, with the result of frequently preventing the latter. The patient is kept in a moist atmosphere at 18 to 20° C. (64.4 to 68° F.), permeated with simple balsamic fumes. A combination of sodium benzoate, senega and citrated caffeine is given, but no antipyretics. Counterirritation, usually with mustard, is employed, and frequently wet cups. In spasmodic bronchitis ether injections are given. Injections of sterile milk are sometimes availed of. For fever, hydrotherapeutic measures are used if required. G. Vidal Jordana (Arch. españ. ped., Sept., 1924).

Intramuscular injections of 0.5 c.c. (8 minims) of ether in the same amount of olive oil, with addition of a local anesthetic, administered in 187 cases of postoperative bronchitis, with very good results. One such injection may with advantage be given daily in all cases of acute or chronic bronchitis unaccompanied by emphysema. Riess (Münch. med. Woch., May 8, 1925).

### Treatment of Chronic Bronchitis.

—The treatment of any patient suffering from chronic bronchitis can be undertaken only after a careful analysis of the condition and a full consideration of the factors causing disease

or discomfort in the particular individual. There may be many factors which combine to maintain the bronchial inflammation or to increase its severity, and these must be met separately.

1. *Circulation* must be maintained and chronic passive congestion decreased or avoided. This may sometimes be accomplished by attention to the cardiac condition, with careful consideration as to the needs of the myocardium as regards regular and judicious **exercise**, **elevation of the head and shoulders** in sleeping, appreciation of minor degrees of decompensation, correction of arrhythmias, careful use of **digitalis** when required, and the proper directions as to environment, particularly as regards **altitude** and **climatic conditions**. Mitral valvular disease predisposes to chronic bronchitis even though compensation be perfect as regards the peripheral circulation. **Hydrotherapy** and **careful exercise** with **avoidance of overexertion**, **out-of-door life** and avoidance of high altitudes in general are favorable agencies. **Purgation** by **saline** is one of the most satisfactory means of relieving the venous embarrassment in beginning decompensation.

In arteriosclerotics **potassium iodide** in small doses provides a useful, in fact, almost indispensable, aid to treatment. From 2 to 5 grains (0.12 to 0.3 Gm.) twice daily is usually sufficient, but even with these small doses the patient should be warned to interrupt the course of administration of the drug if coryza, lachrymation, parotid swelling or skin eruptions appear.

Among the measures for chronic bronchitis are reduction of obesity by **diet** in plethoric subjects and a purin-free diet in the gouty. Free bowel movements should be secured.

In cases with a dry type of bronchitis, secretion may be promoted, aside from drugs, by giving plenty of fluid, *e.g.*, a **milk diet**. In irritative cough, apart from **codeine**, much can be done in strong-willed patients by **cough discipline**, *i.e.*, voluntary suppression of coughing.

On the other hand, when secretion is too abundant, **oil of turpentine**, **terpin hydrate**, and **balsam of Peru** are serviceable agents, which may be both ingested and inhaled. The writer also recommends pure, crystalline **calcium chloride** in doses of 45 to 60 grains (3 to 4 Gm.) a day in solution or tablets. **Belladonna** or **atropine** are likewise of service when intermittently given. Pronounced **reduction of liquid intake** likewise diminishes secretion, especially if water is actually prohibited, at first for one day, then in several-day courses. **Sweating** may also be ordered. To assist in the removal of the secretion, Gerhardts is quoted as advising **ventral decubitus** with the arms crossed behind the back and small **pillows** placed **beneath the forehead and upper chest**; the patient presses his chest against the pillow by extending his feet against the foot of the bed, at the same time breathing deeply. Goldscheider (Deut. med. Woch., Sept. 15 and 22, 1922).

2. The bronchitis may be largely or in part due to a *toxemia*, or exacerbations of increased severity may be brought on by toxic conditions. The question of gout is to be considered and the bowel condition carefully regulated. Sluggishness in the gastrointestinal tract is often reflected at once by an increase in the discomforting symptoms of chronic bronchitis. The **diet** should be chosen with a view to supplying fully the needs of the individual while avoiding toxic effects from improper or excessive feeding. The element of thyroid function in combating toxemia due to infection or

metabolic fault is frequently overlooked. This factor should be carefully considered. The dried **thyroid gland** in doses of from  $\frac{1}{2}$  grain to  $\frac{1}{4}$  grain (0.005 to 0.015 Gm.), *t. i. d.*, may be very useful. **Atophan**, **nov-atophan**, **tolysin** or some other preparation of **phenylcinchoninic acid** is of use in many cases, and **potassium iodide** or other iodide preparation may serve a useful purpose.

In *gouty bronchitis*, with hard, dry cough and dry râles in plethoric, overweight subjects with increased blood-pressure, the writer reduces the diet by at least  $\frac{1}{2}$ , meat being prohibited except once or twice a week and salt and condiments reduced to a minimum. **Water**, 10 to 12 glasses, is taken daily and the bowels kept open with a **saline laxative**. **Potassium iodide**, taken regularly for 2 or 3 weeks, then every other week, and finally 1 week in every month, is of distinct benefit. **Oil sprays** or, occasionally, **steam inhalations** alleviate the cough paroxysms. **Exercise**, such as walking, riding or golf, is most important. Cold air at night should be avoided. Hawes (Boston Med. and Surg. Jour., Aug. 2, 1923).

3. In all cases of chronic bronchitis, *infection* is apt to play a part sooner or later. Some cases are primarily dependent on infection, and this remains the chief factor throughout. Others, dependent on toxemia or circulatory fault, are predisposed to infection. It is important to *avoid infection or reinfection* in all cases of chronic bronchitis. The source of infection may be a tonsillar or sinus focus, an acute rhinitis, a direct inspiratory infection of the bronchial mucosa, or, as is frequently the case, a direct spread may have occurred from a collection of infected matter in a sacculated bronchus, pulmonary abscess cavity or tuberculous cavity.

Careful attention must be paid to the hygiene of the nose and throat in order to avoid acute infection of the upper respiratory tract. Fatigue and undue exposure, irritating dusts and fumes, badly ventilated rooms, coal gas, intestinal toxemias,—any of these factors may change a trivial coryza into a stubborn ethmoiditis or induce an active tonsillitis, in which case the chronic bronchitis will probably become actively infective. Ethmoiditis is stubborn and runs a prolonged course, and if chronic bronchitis is coexistent repeated reinfections of the bronchial tract take place. **Tonsillectomy** should be performed if the tonsils show chronic infection and the patient's condition permits. If chronic post-nasal catarrh is present there is probably an ethmoiditis, and it may be necessary to correct faults of the turbinates or septum in order to secure adequate breathing spaces. **Vaccines** may be of great service in clearing up persistent post-nasal infection.

In chronic bronchitis of *nasal origin*, every abnormal condition of the nasopharynx and sinuses should receive treatment. **Vaccines** are of distinct value, in particular the autogenous variety, and **potassium iodide** is definitely helpful. **Inhalations of benzoin, eucalyptol, menthol, creosote, turpentine**, etc., are of some slight value. For the control of cough, if not productive, **codeine** in 0.03 to 0.06 ( $\frac{1}{2}$  to 1 grain) doses is best. Sometimes the **bromides** in 1 to 2 Gm. (15 to 30 grain) doses prove effective. These drugs should be used sparingly, in particular to prevent loss of sleep. Many patients can be taught to control their cough by the exercise of will power. A productive cough should not be suppressed. As an aid the writer found nothing better than **potassium iodide** and **ipsecac** in some 1 of its fluid forms and in the highest tolerated doses. In cases with asth-

matoid attacks he uses **lobelia** or **belladonna** with **potassium iodide** or **bromide** or both. **Cold sponging** of the chest on arising, the **breathing** and **body-bending exercises** described in drill manuals, and **open air sports** in proper weather are of benefit. Von Zelinski (Med. Jour. and Rec., Feb. 6, 1924).

Local treatment of the nose by a competent practitioner with applications to reduce edema and congestion is frequently essential, and daily care of the nose with bland and non-irritating applications should be practised. **Liquid petrolatum**, **vaseline**, or **dionol** may be applied twice daily. If **camphor** and **menthol** are employed, as is commonly the case, these ingredients should be added in quantities small enough to be devoid of any irritating effect. The organic silver preparations, such as **argyrol**, **silvol** and **arkase**, may be used if they do not irritate the mucosa. **Mercurochrome** is being considerably employed.

For an astringent or shrinking action to promote drainage, **cocaine** is used in 1 to 4 per cent. solution. **Adrenalin**, 1:10,000, is prompt in action, but its application is followed by a secondary congestion. **Ephedrin**, when available, seems to be the most satisfactory drug for this purpose. The relief is as prompt as that experienced with adrenalin, the duration of the local vasoconstriction is much greater, and the phase of secondary congestion seems to be lacking.

Bronchitis is often dependent upon **nasal sinus** infection and shows improvement when such foci are treated. Many such cases neither give any history of nasal disease nor have any local pain or nasal discharge; others have been given treatment for pulmonary tuberculosis. Webb and Gilbert (Jour. Amer. Med. Assoc., March 12, 1921).

If a patient with chronic bronchitis contracts an acute cold it is well to treat the nose at once with a silver preparation such as **argyrol** in 5 per cent. solution or one of the other non-irritating organic preparations, and to give small doses of **atropine sulphate**, *e.g.*,  $\frac{1}{400}$  to  $\frac{1}{600}$  grain (0.00015 to 0.0001 Gm.) at intervals of 15 minutes for several doses if there is any sense of fulness or blockage in the nose. The development of a sinus blockage may be avoided in this way. This phase of the situation has been rather fully considered because the presence of chronic nasal or ethmoid infection has so important a bearing on the question of chronic bronchitis.

**Avoidance of Reinfection from Bronchial Sacculations or Pulmonary Cavities.**—In most cases of severe chronic bronchitis of long standing one can recognize the existence of areas of pulmonary tissue and bronchial tract where drainage is poor and infection tends to persist. From such a focus infection spreads to adjacent bronchi and nearby lung tissue. The prevention of this process depends on adequate and frequent or continuous drainage of the infected focus.

Whether the focus be a bronchial dilatation, a pulmonary cavity or an encysted empyema draining into a bronchus, the effect is the same. Drainage may be aided by **postural treatments** employed several times a day, the patient lying with the head down and the body raised on an inclined surface, assuming the different positions and breathing deeply. These exercises may be remarkably effective if carried out systematically.

Several cases of *putrid bronchitis* treated with **nearsphenamin**. In 1 of these, after 5 months' illness, intra-

venous injections were given in increasing doses (15, 30, 45 cg. at intervals of 7 to 16 days). Fever and expectoration ceased, and the general health improved. There was no history of syphilis. Similar benefit was obtained in a second case. K. Schroeder (*Acta Med. Scandinav.*, Jan. 14, 1921).

**Bronchoscopic treatments** may be employed if a skilled operator is available. The work of Chevalier Jackson and his associates has shown excellent results in many cases in clearing up these pulmonary and bronchial collections. The use of **lipiodol** appears to promise much. **Vaccines** are extremely useful at times, and the results may be strikingly successful. **Autogenous vaccines** are probably preferable to stock preparations in most cases.

Two cases of recovery from *fetid bronchitis* in less than a month following **intratracheal injections** of thick oils, with or without **iodoform**. E. Fronticelli (*Policlin.*, June 16, 1924).

Good effects reported in 6 cases of chronic bronchitis and 2 of *fetid bronchitis* from **intratracheal injections**, administered with a syringe with curved nozzle to be passed into the larynx, of **gomenol**, 5 Gm. (80 minims); **guaiaicol**, 4 Gm. (60 minims); **camphor**, 2 Gm. (30 grains), and **iodoform**, 1 Gm. (15 grains), in 100 c.c. (3½ ounces) of sterile olive oil. N. Parise (*Rif. med.*, Aug. 11, 1924).

To prevent infection of the mucosa by internal medication, by far the most efficacious drug is **creosote**. This agent has a decided effect in improving the symptoms in infective bronchitis, is excreted in the bronchial mucus in sufficient concentration to be detected by its odor in the sputum even when given in small doses, and seems to reduce irritation in the bronchi as well as to exert an inhibiting effect on bacterial growth in

specimens of sputum *in vitro*. Whether this same inhibiting effect is obtained in the bronchial mucosa is, of course, questionable, but it seems reasonable to assume that such an effect may take place in the troublesome collections of infected mucus and exudate which settle in sacculations.

Creosote may be given in solution with tinctures, and well diluted with water, or may be simply dropped into water or milk. The dose which different patients tolerate is very variable, as the taste cannot be satisfactorily disguised, and the drug seems very irritating to the stomach in some individuals. The dose ranges from 1 to 10 minims (0.06 to 0.6 c.c.) 3 times a day. It is said that large doses can be given by dissolving the drug in olive oil. The writer has had no experience with this method of administration. For some years he has used the proprietary preparation known as **calcreose** and found it satisfactory, using from 3 to 8 tablets of 4 grains (0.26 Gm.) each daily. These purport to contain 50 per cent. of creosote. Creosote should be given after meals or with milk. The dosage required for effective action depends on the amount of bronchial secretion; if this be large, a larger dose is required to obtain a satisfactory concentration of creosote in the secretion.

[Sajous, in chronic bronchitis, recommends **saline hypodermoclysis** in small amount, to assist elimination of endogenous toxic products; **reduced or milk diet** for a few days, and **thyroid gland** in 1-grain (0.065 Gm.) doses after each meal, reduced to ½-grain (0.03 Gm.) the second week, but giving in addition **creosote carbonate** in capsules in 10-grain (0.6 Gm.) doses, increasing by 5 grains (0.3 Gm.) weekly until 30 grains (2 Gm.) are taken 3 times daily. To sustain the benefit after recovery, he deems **strychnine** most effi-

cient. The patient should also drink at least 1 quart of **Vichy mineral water** daily to keep up the osmotic properties of his blood and lymph.]

In many of these cases drainage is unsatisfactory because of local or generalized bronchial spasm. This tendency to spasm should be controlled periodically to allow at least intermittent drainage. **Belladonna** or **atropine** in small doses may accomplish this. **Adrenalin chloride** in 1:1000 solution, 3 to 8 minims (0.2 to 0.5 c.c.), may be used if it seems advisable. **Calcium lactate**, 5 to 10 grains (0.3 to 0.6 Gm.) 3 times a day, may be useful.

Reduction of fats and carbohydrates in the diet to the minimum requirements is advised by the writer, but a free allowance of nitrogenous food is to be made. **Vaccines** have assumed the most prominent position in prevention and treatment. An autogenous vaccine is best if the swab can be taken by the bacteriologist and immediately applied to the culture medium; otherwise a stock vaccine may be preferable. The deficiency of lime salts often existing when the expectoration is abundant and albuminous is met by giving soluble lime salts, especially **calcium iodide**, with **milk** and **gelatin** in the diet. When expectoration is scanty and tough, however, with much bronchial spasm, decalcifying agents are indicated, as also in cases with rigid costal cartilages. The **iodides** and preparations of **iodine** and **thyroid** are very useful in the spasmodic or asthmatic type. For troublesome cough, **paregoric** or **opium** and **antimony** are useful. After the acute stage, **apomorphine** and **strychnine** make a good tonic expectorant. In asthmatic attacks, speedy relief is usually obtainable by **percussion between the 4th and 5th cervical vertebrae** and on the **2d dorsal**. If the heart is dilated and its action labored, the **7th cervical** and **2d dorsal vertebrae** should be percussed. In these

procedures the writer places a large cork over the interspace and spines and taps it gently 30 times with a 1½ ounce mallet; this is repeated twice after intervals of 1 minute. Sir James Barr (*Med. Jour. and Rec.*, Apr. 16, 1924).

The **inhalation of steam** impregnated with aromatic medicaments is advocated where bronchial spasm and thick secretion are factors in blocking drainage. **Creosote vapor** is recommended for the purpose, and has been used in very strong concentration.

**Ammonium chloride** may be useful in allaying irritation in the larger bronchi and trachea and in rendering the mucous secretion less viscid; the dose is 3 to 5 grains (0.2 to 0.3 Gm.). **Ipecac** is at times a useful expectorant. Many drugs are recommended for use in chronic bronchitis, but those above mentioned will answer the requirements in most instances. **Guaiacol** salts have been used, but are probably not as satisfactory as creosote and are apt to be depressing. **Tartar emetic** (antimony and potassium tartrate) is useful, but similar in action to and less safe than ipecac. There is no specific treatment for chronic bronchitis, and the satisfactory handling of a patient depends on painstaking analysis of the conditions met with in the individual case and the application of experience, patience and ingenuity in combating them.

An infusion of 1 Gm. (15 grains) of **pilocarpus** leaves—about 1 level teaspoonful—is administered 3 times a day by the writer to excite a more liquid bronchial secretion in bronchitis and asthma without expectoration. Mahlo (*Munch. med. Woch.*, Dec. 21, 1923).

In **bronchorrhea**, **atropine**, **belladonna**, **acids** and **vaccines** may be



tried. In *dry catarrh* with painful cough, the 2d formula given on p. 685, with **iodides**, acts best. **Codliver oil**, with or without **malt**, is often helpful, especially in thin, spare individuals. For retrosternal soreness or muscular pain from coughing the **acetic turpentine liniment** (*Lin. Tereb. Acet.*, B. P.) is one of the best, but other stronger liniments or **iodine ointments** are often useful. In complicating acute bronchitis, the patient should at once be put to bed, however mild the attack may appear at first, **saline expectorants**, **diaphoretics** and **stimulants** given if necessary, and the physical signs watched. Tuberculosis should be suspected in cases in which the summer intermission suddenly ceases. R. A. Young (*Lancet*, Nov. 29, 1924).

**Climatic Requirements.**—**High altitude** and **dry air** are useful to clear up sinus infections and to dry bronchial secretions. This combination of atmospheric conditions tends to make breathing more rapid and greatly increases ventilation and evaporation in the respiratory tract, thereby preventing the accumulation of mucus and lessening the chance of spreading infection.

A remarkable clearing up of chronic bronchitis may take place as the result of a change to a rarefied and dry atmosphere and a high altitude, but it must be borne in mind that the latter condition may be entirely unsuitable for a patient with myocardial insufficiency or valvular disease, or for one with marked tendency to bronchiolar spasm, or where there is a severe degree of pulmonary fibrosis. The dyspnea on exertion which is felt to a much greater degree at high altitudes than at lower levels may have a bad effect on a patient suffering from any of these disorders, and the bronchitis thereby be made worse. If asthma or diffuse bronchial spasm

plays a large part in causing persistence of the bronchitis, or if emphysema is advanced in degree, or if the myocardium shows signs of insufficiency, it is prudent to advise avoidance of high altitudes and recommend an equable climate at a low level.

Warning against allowing chronic bronchitis in *children* to continue indefinitely, lest the condition lead to a mediastinal adenopathy. The child should be sent to a **warm, dry climate** and **sleep with the windows open**. For the cough, **inhalations of eucalyptus**, **tincture of benzoin**, or **balsam of Peru** are to be used, and **counterirritation** to the chest is recommended. The nasopharynx should receive treatment according to any existing indications. **Good food** and **breathing exercises** are both necessary. **Adrenalin** and **pituitrin** are serviceable where the bronchitis is of the asthmatic type. H. Jumon (*Jour. des sci. méd. de Bordeaux*, Apr. 15, 1921).

In selecting a resort for the treatment of bronchitis one must consider altitude, humidity, sunshine, and temperature ranges; likewise, hotel or cottage accommodations, markets or food supply, the opportunities for recreation, and the possibility of getting competent medical attention if necessary.

On the Atlantic Seaboard, in the summer and fall months, the Adirondacks and White Mountains offer a favorable altitude. The mountains of Virginia possess excellent resorts at Virginia Hot Springs and White Sulphur Springs, with a longer season. In the mountains of Carolina, Asheville is a popular resort. For patients with much dyspnea the shore resorts may be favorable. Atlantic City is popular the year round, as much through the convenience of its many hotels, miles of boardwalk and un-

limited wheeling chair service as by reason of its equable climate. Bermuda, Florida and the Bahamas offer excellent climatic conditions with avoidance of the rigor of winter if sea air and low altitude are desired. South Carolina and Southern Georgia have a low altitude and mild winters, and fairly dry air may be found. Augusta and Aiken are examples.

As for high altitudes, Colorado Springs offers hotel accommodations and facilities for medical attention. The "ranches" of Wyoming permit a healthy out-of-door life in the summer for those who are vigorous and not in need of medical attention. Arizona and New Mexico give probably the driest air and greatest amount of sunshine with the widest choice as to altitude, and in Southern California a great range of favorable climatic conditions can be found. These regions offer excellent conditions during the fall and winter months.

When possible, bronchitic patients should move from cold, damp, foggy places to those with an equable, dry, sunny climate, free of cold winds. Where this is impracticable, a change of local residence or of occupation may be helpful. Aside from precautions as to clothing and diet and the use of **vaccines**, the medicinal treatment varies with the type of the condition. In the common *winter cough* or *chronic tracheobronchitis*, a simple expectorant mixture to take occasionally may be all that is necessary:

℞ *Vini ipecacuanhæ*. ℥x (0.6 c.c.);  
*Syrupi scillæ* .... f3j (4 c.c.);  
*Tinct. opii camph.* ℥x (0.6 c.c.);  
*Aquæ chloroformi*,  
 q.s. ad ..... f3j (30 c.c.).—M.

Where cough is irritative and ineffective, a dose of the following mixture taken in hot water may be helpful:

℞ *Sodii bicarb.* .... gr. x (0.6 Gm.);  
*Sodii chloridi* .... gr. iij (0.2 Gm.);  
*Spts. chloroformi*. ℥v (0.3 c.c.);  
*Aquæ anisi*, q.s. ad f3j (30 c.c.).—M.

In cases with marked tracheitis, small doses of **apomorphine**— $\frac{1}{36}$  to  $\frac{1}{20}$  grain (0.0018 to 0.003 Gm.)—are often very useful. In more severe cases with asthmatic dyspnea or copious mucopurulent sputum, a valuable mixture is:

℞ *Potass. iodidi*,  
*Ammon. carb.*, āā gr. iij (0.2 Gm.);  
*Potass. bicarb.* . gr x (0.6 Gm.);  
*Tr. stramonii* .. ℥v-x (0.3-0.6 c.c.);  
*Syr. toluatani* ... f3j (4 c.c.);  
*Aquæ chloro-*  
*formi*, q.s. ad . f3j (30 c.c.).—M.

R. A. Young (Lancet, Nov. 29, 1924).

In searching for a dry climate the bad effects of dust must be considered. Hay fever may be a serious matter for a bronchitic, and the question of pollens should not be forgotten.

**Treatment of Special Types of Chronic Bronchitis.**—*Gas bronchitis* and *influenzal bronchitis* with varying degrees of infection, of emphysema, and of fibrosis must be treated according to the degree of disability found in each patient. For the infection, **vaccines** may be very useful, and a high **altitude** and dry **climate** remarkably efficacious. If emphysema and fibrosis are of severe degree, or if asthmatic symptoms are troublesome, the high altitudes will not be well tolerated. In these cases the general indications for treatment as previously outlined should be met, and in addition increasing **exercise** by setting-up exercises and games such as golf, tennis, riding, etc., should be carried on under careful supervision. The greatest improvement can be obtained by a systematic and regular schedule of exercise in these cases. The possibility of pulmonary tuberculosis must always be kept in view.

In chronic bronchitis following gasping there is often considerable peribronchial thickening; otherwise the pathology is uncertain. Many patients are nervous and apprehensive, and need a frank, encouraging talk; some need a severe talking-to and to be urged to go to work. They are often helped by **potassium iodide**, occasionally with **belladonna**, if expectoration is profuse. Large amounts of **water** and free bowel movements are required. Wind and dust and cold at night are especially harmful. The coughing habit may be broken up by **bromides** as a temporary measure.

Patients with post-influenzal bronchitis need most of all **encouragement**, **iron**, **rest** and particularly a **change**, even if only a short distance away, where business and housekeeping cares can be left behind. Hawes (Boston Med. and Surg. Jour., Aug. 2, 1923).

Postinfluenzal bronchitis is due to secondary infection of a congested, edematous bronchial mucosa, chiefly with 4 types of streptococci. Treatment with carefully prepared and correctly administered **autogenous vaccines** containing these organisms for a varying period yielded results after failure of all other measures. Hurwitz (Cal. and West. Med., Dec., 1924).

*Bronchitis due to cardiac disease* or complicated by severe degrees of cardiac insufficiency must be treated as a cardiac condition. **Low altitudes** are usually more favorable. **Digitalis** and **nux vomica** may be of great service.

**Hydrotherapeutic measures**, such as **Nauheim baths**, best given in a sanitarium or hospital, may be useful. **Avoidance of overexertion** must be enjoined.

*Bronchitis following pneumonia* may be persistent and complicated by unresolved exudate, which seems to cause bronchial irritation. This is

probably within the pulmonary vesicles in large part, but there is also a peribronchial exudate which can be seen by means of the X-ray. In these cases an asthmatic tendency is apparent, together with signs of a chronic bronchitis or frequent recurrence of acute bronchitis. The therapeutic use of the **X-ray** in these cases may result in a prompt clearing up of signs, symptoms, and X-ray evidence of disease, even though the condition has existed for many months following pneumonia.

The treatment of *syphilitic bronchitis* is that of syphilis. Care must be taken to exclude, so far as is possible, the coexistence of tuberculosis. If this infection is present moderate doses of **mercury** are well tolerated but the use of iodides may be disastrous. Experience with **bismuth** has seemed to show that it is an extremely satisfactory means of meeting this difficult situation.

In *plastic or fibrinous bronchitis* there seems to be no special form of treatment which is established as successful. These patients must be treated symptomatically. The use of **iodides** is said to aid in loosening the casts, thus relieving dyspnea. **Arsenic** has been recommended.

Case of a boy of 7 years with dyspnea, particularly at night, and expectoration of tracheobronchial casts. The X-ray showed the superior mediastinum filled with a dense shadow, blending with the heart shadow below. The cast formation in the bronchi is ascribed to mediastinal gland enlargement (secondary to infection of the air-passages higher up), with involvement of the thymus by contiguity, thus impeding the pulmonary venous circulation by compression and leading to leakage of serum into the trachea and

bronchi. Two **X-ray** exposures of the mediastinal enlargement reduced it considerably and the expectoration of casts ceased. P. B. Mulligan and R. D. Spencer (Jour. Amer. Med. Assoc., Mar. 8, 1924).

In chronic bronchitis associated with marked degrees of *pulmonary fibrosis*, *emphysema* or *anthracosis*, **low** or **moderate altitudes** are usually desirable. **Iodides** are useful, but care must be taken to exclude the possibility of a tuberculous infection, which renders the use of iodides hazardous.

### BRONCHIECTASIS.

This condition has already been briefly discussed in connection with chronic bronchitis resulting from influenza. While influenza seems to have been the most common cause, at least during recent years, bronchiectasis occurs as a result of many other conditions.

**SYMPTOMS.**—The symptoms depend on the degree of dilatation and size and number of the cavities, on the nature and degree of secondary involvement, and most of all, on the degree of accompanying pulmonary involvement and bronchitis.

The chief symptoms are dyspnea, cough and expectoration, constitutional symptoms of infection, and repeated attacks of bronchopneumonia, generally of mild degree, with chronic bronchitis.

Where a large cavity or cavities exist, the cough and expectoration may be intermittent, with remissions during which the symptoms are not troublesome, followed by exacerbations of uncontrollable cough and copious purulent expectoration. Surprisingly large amounts of pus are expectorated during these exacerbations. The sputum may be frankly

purulent or contain large quantities of mucus. It may be blood-tinged, or actual hemorrhage may occur. The sputum may be putrid and extremely offensive at times. The very fetid sputum is apt to be of a thin, watery consistency. An irritative laryngitis usually persists while the sputum maintains this putrid character, and the resulting cough, throat pain, and gagging add greatly to the patient's discomfort.

Copious expectoration is not a necessary feature of bronchiectasis, which the writers do not regard as being always secondary to chronic bronchitis or bronchopneumonia, but rather a primary disorder, often of unaccountable origin. As in 2 cases observed, it may be manifested mainly in repeated hemoptysis without expectoration. No tubercle bacilli were found in these cases. In 1 case the customary signs of bronchiectasis with profuse expectoration appeared, however, when the patient was exposed to influenza cases. The hemorrhage in bronchiectasis is occasionally fatal. The condition may date back to infancy, or even be congenital, or, when latent, may be brought into activity by pneumonia, influenza, measles or whooping-cough; asphyxiating gases are also a cause. F. Bezançon, M. P. Weil, R. Azoulay and E. Bernard (Presse méd., Feb. 20, 1924).

Allusion to an important sign of bronchiectasis described by Lemon, *viz.*, the ability of the patient to produce sputum at will by assuming a head-down position. Hedblom (Surg., Gyn. and Obst., June, 1924).

Where there is a history of copious expectoration at more or less infrequent intervals bronchiectasis must be suspected. In multiple involvement of the smaller bronchi the symptoms are different in that secretion or pus is being constantly discharged into the larger tubes and expectorated.

Recurrent infections of lung tissue are the rule, and the subjects of bronchiectasis are apt to suffer from time to time with febrile attacks due to this complication.

A fairly large proportion of large bronchiectatic cavities eventually rupture into the lung with the production of pulmonary gangrene or abscess as a terminal process.

The *physical signs* are those of bronchitis, usually accompanied by some degree of emphysema if the case is one of long standing. There is practically always involvement of lung tissue in addition, so that dulness to percussion and increased fremitus with cough or bronchial breath sounds may be heard in the region of the bronchial dilatation.

The physical signs of an apical bronchiectasis are similar to those of pulmonary tuberculosis with cavity. Bronchiectasis is more apt to occur in the base of the lung, and if the apices are relatively clear with basal involvement, bronchiectasis must be considered.

**ETIOLOGY AND PATHOLOGY.**—The habitual inhalation of irritating dust, as in grinders and miners, is a frequent cause. Thus, Landis has mentioned that of 21 potters under observation by him, evidence of bronchial dilation was present in 10. Foreign body in a bronchus is also a common cause, according to Chevalier Jackson, who has observed and described many such cases. Pneumonia, apart from influenza-pneumonia, already mentioned, is a common cause. Stricture of the bronchus due to syphilis may cause bronchiectasis. Pulmonary tuberculosis, pulmonary fibrosis, pleural effusion and pulmonary collapse are other conditions which may result in bronchiectasis.

In a series of 108 cases studied post-mortem, the etiologic conditions were: Chronic bronchitis, 41; pleurisy with pneumonia, 27; bronchial obstruction from various causes, such as new growth, foreign body, aortic aneurysm and syphilitic stenosis, 37. The principal causes of death were: Bronchopneumonia, 34; exhaustion, 34; exhaustion and asphyxia, 8; intracranial abscess, 15; and hemoptysis, 5. E. Jex-Blake (Brit. Med. Jour., May 1, 1920).

Disease of the nasal accessory sinuses is an important etiologic factor. Patients with bronchiectasis usually have a well marked sinusitis, and the degree of bronchial infection is usually in proportion to the amount of sinus involvement, the well advanced cases of bronchiectasis having a pansinusitis. Study of a series of cases showed that the majority of them started with nasal trouble and cough during childhood. W. V. Mullin (Ann. of Otol., Rhinol. and Laryngol., Sept., 1921).

The wall of the bronchus may be weakened by ulcerative and inflammatory damage to the structure from within, as in influenza or foreign body cases; or the withdrawal of outward support, as in pulmonary collapse and fibrosis, may allow a dilatation under stress of coughing and straining.

The dilatations of the bronchi occur in various parts of the bronchial tubes, and may be saccular, fusiform or diffuse enlargements. They are usually multiple, though single cavities may occur, particularly as a result of the lodgment of a foreign body. It is not unusual to find numbers of the smaller divisions uniformly enlarged, with involvement of the bronchial supply of a large part of the lung on both sides.

**DIAGNOSIS.**—Pulmonary tuberculosis is the condition most frequently confounded with bronchiectasis and, indeed, bronchiectasis frequently develops in chronic fibroid tuberculosis. If the sputum is puru-

lent, a number of negative sputum specimens are evidence in favor of the condition not being pulmonary tuberculosis. A history of influenza at the onset of trouble is in favor of the diagnosis of bronchiectasis. Foreign bodies in the bronchus may be found by X-ray or bronchoscopic examination. Pulmonary abscess is apt to run a more constant febrile course.

Difficulties are met with in differentiating *apical* bronchiectasis from tuberculosis. The symptoms, physical signs and radiogram may all suggest tuberculosis when it does not, in fact, exist. On the whole, a negative tuberculin test and prolonged observation of the case are the best means of differentiation. A. Bauer (Beit. z. Klin. d. Tub., Nov. 1, 1923).

A severe degree of clubbing of the fingers coming on rapidly is in favor of bronchiectasis, as this condition seems to be responsible for the most marked examples of the so-called pulmonary osteoarthropathy which are met with.

In a well-marked case bronchiectasis can readily be observed by *bronchoscopy*, the bronchial dilatations alternating with contractions, with the walls chronically inflamed, possibly eroded or ulcerated and smeared with foul pus. In doubtful cases *bismuth subcarbonate* may be insufflated through the bronchoscope and a *stereoröntgenogram* made. Chevalier Jackson (Trans. Amer. Acad. of Ophth. and Otol., 1923).

Alluding first to the deficiencies of ordinary X-ray study in bronchiectasis, the writers point out that after intratracheal injection of *lipiodol* (a vegetable oil containing 40 per cent. of iodine), bronchial dilatations are plainly pictured. The procedure proved valuable in distinguishing cavities formed by a dilated bronchus or communicating widely with a bronchus, as in bronchiectasis or peribronchial abscess with destruction from the bronchus out-

ward, from cavities that have opened only secondarily into bronchi, as in lung abscess or pleural cavity, from which the *lipiodol* usually cannot pass into the bronchus through the narrow fistula formed. E. Sergent and P. Cottenot (Bull. de l'Acad. de méd., Jan. 22, 1924).

Description of the use of a curved trocar and cannula to be passed into the trachea through the cricothyroid space under local anesthesia; 5 c.c. (80 minims) of 1 per cent. procaine are then injected into the trachea, followed by *lipiodol* to the amount of 8 to 10 c.c. (128 to 160 minims) in children of 7 to 14 years. Only 3 c.c. of *lipiodol* per minute are injected. The X-ray exposure immediately follows the injection. Armand-Delille, Duhamel and Marty (Presse méd., May 14, 1924).

Bronchiectasis can be diagnosed best by correlating the findings in X-ray plates taken with the patient in various positions with the history and the findings of physical examination. The writers do not advocate the use of bismuth subcarbonate, bismuth in oil, or *lipiodol*, as these substances are apt to cause foreign-body complications. Instead, in selected cases, they use a *diagnostic pneumothorax*. In bilateral bronchiectasis this will show which of the lungs is the more diseased. Characteristic of bronchiectasis are triangular densities with their apices at the hilum. After the first X-ray plate is taken, postural drainage should be instituted. Subsequent plates will give information in relation to the size of the bronchiectatic area. J. J. Singer and E. A. Graham (Amer. Jour. of Roentg., Jan., 1926).

**TREATMENT.**—In this condition the value of proper climate conditions is specially marked. Good ventilation is necessary, and altitude and dryness of the atmosphere should be sought.

**Creosote** is of particular service and should always be tried.

According to Marini, **tannic acid** and **calcium biphosphate** exert a favorable effect and deodorize the expectoration. He gives 4 powders daily, each containing 4 grains (0.25 Gm.) of each drug. If hemoptysis occurs the amount of tannic acid may be increased by one-half. During this treatment only water should be drunk.

**Vaccines** have given remarkable success, and an **autogenous vaccine** should be tried over long periods.

**Bronchoscopic treatments** give excellent results in connection with **vaccine** treatment. If bronchial spasm constitutes a feature of the case, **atropine** or other antispasmodics may be serviceable. **Iodides** may be of help, but may increase secretions and render the keeping of the cavities dry a more difficult matter.

**Exercise** is useful in maintaining drainage, but overexertion is dangerous as it lowers resistance, and long periods of **rest** may prove necessary.

**Postural treatment** is essential. The problem to be solved in these cases is that of draining the cavities and maintaining a dry condition therein. Gravity is utilized in emptying the cavities by having the patient assume a position with the head downward, lying on either side and breathing deeply. Such exercises are to be gone through 2 or 3 times daily.

In localized bronchiectasis in the lower pulmonary lobes, the writer obtained excellent results from **postural treatment**. After the usual discharge of sputum every morning, the patients remained in the horizontal position for 2 hours. Later the foot of the bed was raised 30 cm. (12 inches) in addition, to enhance the detergent action of gravity. H. Schaefer (Klin. Woch., Feb. 5, 1923).

Another aid to emptying and possibly collapsing the cavity is found in the employment of **therapeutic**

**pneumothorax**. Artificial pneumothorax or **pulmonary collapse by rib resection** should be advised only after careful consideration and the securing of expert opinion.

Review of 65 cases treated by **artificial pneumothorax**, including 5 personal cases. Improvement or recovery resulted in about  $\frac{2}{3}$  of the cases. In 3 of the writer's cases the pneumothorax was only partial, but much betterment resulted in 2 and recovery in 1. In another case lung collapse was maintained for 6 years, with resulting great reduction of sputum and disappearance of its odor. In 61 per cent. of the total of 65 cases the disease was known to be unilateral and in 18 per cent., bilateral. Attempts at bilateral pneumothorax were not successful. J. Tillman (Acta med. scand., Oct. 4, 1923).

Ten cases of diffuse unilateral bronchiectasis treated by **extrapleural thoracoplasty**, which was performed in 4 to 7 stages under nitrous oxide-oxygen anesthesia, followed by alcohol injection of the intercostal nerves. There were no deaths, and 6 cases were restored to good general health, 3 being practically free of symptoms, while 3 still raised 30 to 60 c.c. of sputum in the 24 hours. C. A. Hedblom (Arch. of Surg., Jan., 1924).

The treatment of bronchiectasis is a long-drawn-out process, but often is successful. Cases of bronchiectasis may show improvement with almost complete disappearance of symptoms over long periods of time, although they tend to retrogress from time to time. They require patience on the part of both patient and physician.

Where adhesions prevent success with artificial pneumothorax, **opening of the chest** and **severing the adhesions** will usually be followed by the desired retraction of the bronchiectatic lobe. Additional compression can be obtained by suturing a flap of pleura and muscle around the isolated tube, the subsequent contraction of

the scar tissue apparently compressing the lobe much like artificial pneumothorax. In thoracotomy, if **rib resection** is first done, additional compression can be secured by applying a pad to the soft parts over the affected lobe. Singer and E. A. Graham (Jour. Mo. State Med. Assoc., Sept., 1922).

**Lobectomy** is the only procedure offering a chance of complete relief from all symptoms in advanced cases. The author describes a modified lobectomy performed with the actual cautery. This was carried out clinically in 3 cases without mortality or serious reaction. At the 1st operation a flap of skin and muscle is turned up and portions of several ribs removed. Thereafter, in as many stages as desired, without any need of anesthesia, all the diseased tissue is removed by successive evacuations with a large soldering iron, heated to a red heat, into the lung tissue. In 1 case nearly all of 1 lung was thus removed. The remaining eschar sloughs away in about 10 days. No trouble from hemorrhage was experienced. The cavity and bronchial fistulas gradually obliterate themselves. Healing is hastened by **heliotherapy**. E. A. Graham (Jour. Amer. Med. Assoc., Sept. 22, 1923).

### **Vaccine Therapy in Chronic Bronchitis and Bronchiectasis.**

In infective bronchitis the use of a vaccine is frequently very successful. To explain the success of this expedient it is not necessary to attribute to the vaccine any power of combating the specific infecting agent. It may be that antibodies are increased by the use of vaccine, and it is probable that such is the case when certain strains of organisms are used as the antigen. Even in the absence of such action, it is possible that tissue tolerance for bacterial toxins is gradually increased so that infection ceases to cause local reactions of a

severe degree. Thus, if the nasal mucosa does not become engorged and swollen as a result of a slight infection, a sinusitis may be avoided and ethmoid drainage satisfactorily maintained, and if the bronchial musculature does not respond to the presence of infection by spasm one of the important factors in preventing drainage of the bronchial tract will thereby have been taken care of.

The writer has treated many cases of chronic bronchitis and bronchiectasis with the aid of **autogenous vaccines** prepared by Dr. John Laird, Director of Laboratories for the Pennsylvania State Department of Health. He uses a mass growth from the sputum grown rapidly on various media, the resulting growths being combined in an emulsion approximating 10 billion organisms per cubic centimeter. For convenience the vaccine is measured in drops. The dosage is started at 1 c.c. of a 1:100 dilution, and the dose doubled at each subsequent injection unless reaction indicates a change in dosage. The interval between treatments is 4 or 5 days at first; later, 7 to 10 days. The dose is usually carried up to a point where 10 to 15 drops are well tolerated.

Vaccines constitute the most potent means of curing and ameliorating, as well as of preventing, chronic bronchitis. The writer uses **autogenous vaccines**; stock vaccines are not likely to meet with more than a modicum of success. The treatment must be continued at least 3 months, the object being to establish a high degree of resistance. The intervals between the early tentative doses should be 5 days; when reaction has been established this may be lengthened to 7 days. Gradually cough and expectoration should entirely disappear. Cases with an associated bronchiectasis benefit the



most. Preferably a new vaccine should be prepared at least once during a 3-months' course. In a given patient the bacteriology of successive winter recurrences is seldom identical. J. O. Symes (Brit. Med. Jour., Dec. 15, 1923).

ROBERT G. TORREY,  
Philadelphia.

## BRONCHITIS, CAPILLARY.

See BRONCHOPNEUMONIA.

**BRONCHOMYCOSIS.**—Increasing attention is being directed to bronchial disorders of mycotic origin, i.e., due to fungi. The commonest forms appear to be those due to the genus *Monilia*; hence the term **bronchomoniliasis** which has been applied to many of these cases. The term **broncho-oidiosis** has been used practically as a synonym to bronchomoniliasis, Castellani, e.g., having applied this term to the various types of bronchitis and bronchoalveolitis due to fungi occurring in the tropics. According to Brumpt, the foremost French parasitologist, however, the generic term *Oidium* has been incorrectly applied in designating certain organisms parasitic to man, and should be reserved for certain Ascomycetes parasitic to plants such as the grape-vine, cereals, peach-tree, rose, etc.

According to Mendelson, bronchomoniliasis, also termed *bronchoendomycosis*, is probably more common in the United States, particularly in the South, than has been thought. It is due especially to *Monilia tropicalis*, which was found by Castellani in numerous cases from Ceylon, South India, and the Malay States.

**SYMPTOMS.**—Two types, mild and severe, have been described by Castellani. In the *mild type*, there is merely cough, muco-purulent expectoration, and perhaps a few coarse râles. After several weeks or months, recovery occurs, or the condition may pass into the *severe type*, which is closely similar to tuberculosis, with emaciation, hectic fever, muco-purulent and bloody expectoration, occasionally hemoptysis, and dullness, fine crepitations, and pleural rubbing. This form is frequently fatal. Cases of intermediate severity also occur.

Attention has been called by E. Steinfield (Jour. Amer. Med. Assoc., Jan. 12, 1924) to the existence in the United States

of bronchomycosis of a mild, chronic type, particularly associated with certain cases of asthma and chronic bronchitis. Of 15 cases, 7 were men and 8 women, ranging in age from 25 to 60 years. All were residents of Philadelphia, and with 1 exception, gave negative histories and tests as to sensitization to proteins. The symptoms were more or less constant cough, with relief during periods of free expectoration, and paroxysms of expiratory dyspnea, often at night, with audible wheezing. During active stages sonorous and sibilant râles were usually audible over both lungs. The absence of percussion changes, presence of eosinophilia (e.g., 6 to 8 per cent.), and fairly prompt disappearance of signs under treatment were in marked contrast to the severer lung diseases.

The symptoms are somewhat similar, according to Castellani, whatever fungus is the cause. The infection may take place from man to man and also probably by the fungi living saprophytically in nature.

**PATHOLOGY.**—The lesions are very similar to those of tuberculosis, consisting typically of small white masses or mycotic "tubercles." Necrosis does not appear to occur, although these "tubercles" receive no blood-supply. They seem to consist of old connective tissue.

In Steinfield's cases, the sputum usually showed, embedded in mucus, chalklike particles or actual islands of yeast colonies, occasionally amber-colored. The high-power objective often showed these as consisting of globular, fatlike spores; at times, during severe stages, of hyphæ and mycelia. Cultures of the particles in Sabouraud's maltose agar adjusted to pH 5.2 yielded yeasts of the genera *Monilia*, *Cryptococcus* and *Endomyces*.

**DIAGNOSIS.**—Severe cases of the condition are distinguished from *pulmonary tuberculosis* by the absence of the tubercle bacillus from the sputum and negative guinea-pig inoculations. Sometimes, however, mixed cases of tuberculosis and moniliasis occur, showing both germs. Bronchomoniliasis of primary nature is also to be distinguished from *thrush* infection, *Monilia albicans*, which may extend secondarily from the mouth down the respiratory tract in cachectic patients—cancer, diabetes, tuberculosis, etc.

A positive diagnosis of moniliasis is made by finding the causal organism in the sputum. In fresh sputum, stained with methylene blue, the organism appears as spore-like, roundish or oval cells of 4 to 6 $\mu$  size, occasionally with mycelial strands.

Cultures are readily obtained on Sabouraud's maltose agar or glucose agar, and even on ordinary agar. Slightly acid media are best. According to Castellani, all species of *Monilia* grow fairly well on gelatin.

The growth on agar is creamy white and consists of globular, yeast-like cells.

The tropicalis species is identified especially by its sugar reactions.

**TREATMENT.**—In mild and intermediate cases **potassium iodide**, 10 to 20 grains (0.6 to 1.2 Gm.) 3 times daily, soon yields benefit and causes disappearance of the monilia from the sputum. **Sajodin** in the same doses in cachets, and injections of **lipiodol**, 32 minims (2 c.c.) for 4 consecutive days, repeated at intervals, have also given successful results. The severe type of case is much more refractory. Aside from the iodide, **balsams** may be tried, together with **nourishing diet** and other measures commonly employed in tuberculosis.

In Steinfeld's cases the iodide proved of great value in the dosage above mentioned. In several cases, **pix pini**, 15 minims (1 c.c.) a day or more, was efficacious. **Vaccines**, prepared from the cultured yeasts after the method of Michel and injected in doses of 0.1 or 0.2 c.c., increased to 1 c.c., seemed to further the improvement. In all cases, the sinuses and tonsils should be examined for abnormalities or disease.

Three cases of chronic bronchitis in which fungi were found in the sputum. **X-ray** treatment led to disappearance of the fungi and striking improvement of the bronchitis. Howe and Schmidt (N. Y. State Jour. of Med., Jan. 23, 1925). S.

**BRONCHOPNEUMONIA.**—**SYNONYMS.**—Lobular pneumonia, catarrhal pneumonia, bronchovesicular pneumonia, disseminated pneumonia, bronchoalveolitis, bronchoalveolar catarrh, peribronchitis (Balzer), capillary bronchitis, suffocative catarrh.

**DEFINITION.**—An inflammation of the terminal bronchus and the air-vesicles which make up a pulmonary lobule, usually affecting many comparatively small areas of contiguous and neighboring lobules in both lungs and in all lobes.

**VARIETIES.**—There are recognized two principal types of the disease: the *lobular*, in which the dissemination of the morbid process and the distinctly lobular involvement of the alveoli can be readily demonstrated, and the *pseudolobar*, in which the massing and extent of the affected areas give a resemblance to the consolidation of croupous or lobar pneumonia. To these may be added that type which was, at one time, clinically distinguished as *capillary bronchitis*. Cases may also be separated according to their *origin* and *mode of onset*. Those which are the first and independent result of infection or injury are termed *primary*. They are less common than the *secondary* cases, which supervene upon acute or chronic infectious maladies, especially whooping-cough, the exanthemata, and tuberculosis, or which complicate widespread infections of various kinds. Both primary and secondary cases may develop *frankly* or *insidiously*. Also *terminal infection* in Bright's disease, diabetes, etc., and even in simple asthenia of old age, may take this form.

**SYMPTOMS.**—As the severity of the pathological processes varies greatly in different cases, the symptoms have corresponding variability. Necessarily, too, the primary and secondary cases differ in onset and development. In some primary cases the general symptoms are so slight that the patient walks around attending to his usual affairs, or, if a child, plays

about, with but slight complaint except of cough, or, as is likely to be said, of "cold." This is not infrequent at the beginning of an attack of influenza, which may afterward prove quite severe, if unattended to; and it is the rule in the early stages of tuberculosis. The mistake of looking upon the case as one of simple bronchitis may thus easily be made.

Elevation of temperature, often surprisingly great, will, however, be discovered upon thermometrical examination; percussion and auscultation of the chest will reveal some of the characteristic physical signs. There may be slight pain in the chest, especially if there be pleural involvement, and this is more common in influenza and tuberculosis than in other varieties of the affection. In other cases the symptoms, though rarely, except in influenza, sudden in onset, become quite severe from the first; there is prostration, with high fever, rapid pulse, headache, restlessness, pain in the chest, and respiratory distress, with quickened breathing, cough, and usually expectoration; though in children in whom the morbid process ensues as a sequela of some infectious fever the cough is at first dry and harsh. In infants and young children, moreover, there is often difficulty or even impossibility of expectoration, so that the moist sounds of air passing through the mucus retained in the windpipe and bronchi may be audible even to the casual observer, and there is then considerable distress in respiration, often approaching suffocation, thus giving rise to the common synonym of capillary bronchitis: suffocative catarrh. The matter expectorated is not, as a rule, blood-stained, but varies much in its physical characteristics. It is usually mucoid; sometimes, and especially

in tuberculosis, mucopurulent; and in influenza often resembles boiled sago sprinkled with coal-dust. I have come to look upon this black discoloration of the influenzal sputum as quite characteristic. Whether it is common, outside of dusty cities, I do not know. The appetite is impaired, the tongue coated, the lips red and dry at first, afterward cyanotic. The skin is dry and hot. In cases beginning insidiously, the symptoms may suddenly develop after a previous unmarked stage of general depression, or the distress may be of gradually increasing severity.

Both sudden and gradual onset of bronchopneumonia is observed during the progress of the exanthemata or whooping-cough. Although in measles catarrhal symptoms mark the onset of the malady, they may clear up, and bronchopneumonia be manifest only when convalescence should be declared.

Out of 56 cases studied by Nicoll, vomiting occurred 6 times, convulsions in 5; chills were noted in 2 cases, and looseness of the bowels was frequent. The writer believes that the most noticeable remittency in temperature is seen in the cases in which the influence of the streptococcus predominates. A critical ending occurred only 9 times in 167 cases. The diagnosis between bronchopneumonia and meningitis is often difficult, for, in both, spasm of groups of muscles, tache cérébrale, Kernig's sign, Brudzinsky's sign, and rigidity of the neck may occur.

The *Streptococcus hemolyticus* is capable of causing fatal epidemics of interstitial bronchopneumonia. The condition arises with or without such predisposing causes as measles, but seems especially severe after that disease. There is often also a diffuse, patchy, lobular pneumonia in which the streptococcus is finely scattered in the alveolar exudate. Such areas may be confluent and resemble lobar

pneumonia. Ulceration of the vocal cords and epiglottis and empyema are frequent complications. MacCallum (Jour. Amer. Med. Assoc., Aug. 31, 1918).

Experiments to ascertain in what particular portion of the bronchial tree the vibrations audible in bronchial breathing arise. In the smaller tubes of 3 or 4 mm. diameter, overtones are too marked. Conditions in and around the largest bronchi are likewise unfavorable. The bronchi in which bronchial breathing actually arises are those of diameters ranging from 5.5 to 10 mm. P. Martini and H. Mueller (Deut. Arch. f. klin. Med., Oct., 1923).

Physical examination at first, especially in children, may fail to reveal dullness or even blowing breathing, but there will be discovered, scattered over both lungs and often more frequent and more extensive at the bases, showers of fine, subcrepitant râles. Sibilant rhonchi may likewise be heard. In the course of a day or two, sometimes later, scattered areas of dullness associated with bronchial or vesiculobronchial breathing, and moist râles, and sometimes with absence of breath-sounds, indicating atelectasis, are discovered. Of these some are constant and others appear and disappear: shifting dullness. They are found upon both sides, and may be numerous and small, or few and extensive. Sometimes they are massive, involving the greater portion of a lobe or of a lung. These massive areas are constant, and over them the breathing is distinctly bronchial, closely resembling that of lobar pneumonia. Bronchophony may be present. In tuberculosis, what I have termed "the isolated apex sibilant rôle" is quite characteristic. An apex pleuritic friction is sometimes heard, and usually as the case progresses there develop characteristic crackling, and the liquid râles indicative of softening.

As these signs develop, indicating extension of the local morbid processes, the symptoms become correspondingly severe. Dyspnea increases and the respiration rate rises, with children reaching 60 or 70, with adults rarely exceeding 50, and usually remaining below that number. Cyanosis now becomes manifest. There may be supra-sternal and infrasternal retraction. At first, in severe cases, the children exhibit great restlessness and anxiety, but, as asphyxiation progresses, sensation becomes obtunded, drowsiness increases, and, while the breath becomes more gasping, the efforts to obtain air diminish. The heart becomes weaker; the right ventricle is evidently distended; the pulse is small, feeble, and fluttering, and death may occur from cardiac paralysis or from exhaustion. Sometimes there is delirium, cephalalgia, retraction of the head, and tenderness of the scalp and neck, apparently indicating meningeal complications, and convulsions may occur; at other times there is constant or intermittent delirium, with jactitation, and this seems to be rather toxicemic than due to cerebral inflammation.

Recovery may take place even in apparently desperate cases, and the symptomatic changes may be as sudden as in lobar pneumonia, though usually the process is gradual, but rapid. The duration varies from about ten days to about three weeks. In cases delayed beyond this the suspicion of tuberculosis or localized empyema becomes strong. Some cases, however, which are not clearly tuberculous, run a remittent or subacute course, and others gradually take on a chronic type.

**DIAGNOSIS.**—It is the frank primary cases and those of insidious onset that cause difficulty in diag-

nosis. Cases clearly secondary to whooping-cough, the exanthemata, etc., usually tell their own story.

There used to be much written concerning the differential diagnosis of capillary bronchitis and bronchopneumonia. Post-mortem investigation has shown that the differentiation is impossible, for the two conditions usually coexist. The difference is symptomatic only, and affects treatment only as this is guided by symptoms.

It is a question whether in children all cases of apparent acute bronchitis should not be considered, at least potentially, as bronchopneumonia. Similar caution as to the aged is also desirable. A tendency to recurrence is always suspicious. Apart from this the physical signs of consolidation differentiate, and in simple bronchitis, moreover, the marked depression is absent.

Typhoid fever sometimes begins with signs of bronchopneumonia. Caution and careful observation will usually direct attention to the true state of the case. As it progresses the characteristic temperature, the splenic enlargement, the rose spots, clear up the diagnosis.

Apart from the recognition of influenza as the basic condition—a fact frequently overlooked when epidemics are not manifest—the chief difficulties are to determine whether or not lobar pneumonia exists in a case presenting massive areas of dullness, and to determine whether or not a case of recognized bronchopneumonia is tuberculous.

**Lobar Pneumonia.**—As to lobar pneumonia, it is to be remembered that this is less frequent, though not altogether rare, in the aged and in chil-

dren under 5 years of age. Between 5 and 60 there is little diagnostic dependence to be placed on age. The mode of onset is usually different, lobar pneumonia developing abruptly with chill, lobular pneumonia coming insidiously and, as a rule, being a secondary infection. Lobar pneumonia is usually one-sided and limited; bronchopneumonia is usually scattered over both lungs. Even when lobular foci are massed, it is more common to find the other side involved than in lobar pneumonia. Yet there are cases, severe and often fatal, of lobar pneumonia beginning insidiously and extending from one region of the lung to another and from one side to the other, or even bilateral from the beginning; so that these points of distinction are far from absolute. The physical signs are of greater certainty. In lobar pneumonia the physical signs of consolidation are persistent until resolution begins. Some shifting dullness is usually found in bronchopneumonia. The râles of lobular pneumonia are rather subcrepitant than crepitant, and the ringing râle is much more frequent than in lobar pneumonia. Rusty sputum is the rule in lobar pneumonia, the exception in lobular pneumonia. Pneumococci may be present in pure culture and, at least, commonly predominate in lobar pneumonia; other organisms are frequent in bronchopneumonia. Yet, this is by no means an infallible test. A high leucocytic count is usually in favor of lobar pneumonia; but a low count does not imply its absence. Lobar pneumonia most frequently terminates by crisis from the fifth to ninth day; bronchopneumonia is more prolonged and subsides by lysis.

Under the appellation *protracted unilateral bronchopneumonia of lobar*

*distribution*, the author draws attention to a condition characterized by a lesion in the lower pulmonary lobe, usually on but one side only. The disease, as he describes it, starts either acutely, like a cold or grip attack, or insidiously, so that the patient is unable to give the date of onset. He complains of cough, slight fever and a tendency to tire easily. The sputum, variable in amount, is usually frothy and sometimes blood-streaked. At times a frank hemorrhage occurs. Slight pain, either pleural or muscular, may be present. The appetite remains fair, but as a rule there is loss of flesh, though, on the whole, the general health suffers but little even after months of illness. The percussion note is slightly impaired and the voice sounds usually somewhat augmented. Most striking and unexpected is the presence of a superabundance of moist, crackling râles, limited to the lower lobe. They resemble those of pulmonary edema, but are a little louder and less uniform. The X-ray findings are usually very slight, in marked contrast to the auscultatory signs. The duration is seldom less than 2 or 3 months. The condition seems due to an infection of low virulence. Tuberculosis and typhoid fever are the most frequent incorrect diagnoses. The treatment is symptomatic, with simple sedatives for troublesome cough, avoidance of exposure and abstention from work. A change of climate is sometimes beneficial. D. Riesman (Penna. Med. Jour., Jan., 1922).

At the time of the influenza epidemic of 1918, the writer, carrying out 84 autopsies in cases that had died of the thoracic complications of influenza, found the following conditions: Fibrinous lobar pneumonia, 30; ordinary bronchopneumonia, 26; hemorrhagic bronchopneumonia, 14; pneumonia with hemorrhagic hepatization, 8; primary suppurative pleurisy, 4, and primary pericarditis, 1. The hemorrhagic and suppurative form of pneumonia is seldom witnessed apart from influenza epidemics. The hemorrhagic hepatization type is also a special appurtenance

of influenza. P. Menetrier (Bull. de l'Acad. de méd., Feb. 7, 1922).

A study of cases of pneumonia in infants and children received in a hospital showed 199 cases of bronchopneumonia as against 218 of lobar pneumonia. In contrast to figures previously recorded, the mortality from bronchopneumonia was but 7.1 per cent., as against 12.9 per cent. for lobar pneumonia. X-ray examinations showed distinct markings in 247 cases, and are regarded as indispensable in the diagnosis of doubtful cases. In bronchopneumonia the leukocyte count was relatively low, while in lobar pneumonia it was always high. R. D. Moffett (Arch. of Ped., Nov., 1924).

#### **Tuberculous Bronchopneumonia.—**

This form is much more common both in adults and in children than was formerly supposed. Many cases of so-called bronchitis in infants and children are of tuberculous origin, perhaps extending from the glands. At Jefferson Medical College Hospital, where I saw many children and adolescents in the years 1884 to 1887, I made inquiries as to the antecedents of many of the cases of "cough" of various kinds, and found that there could be separated a group of cases of *recurrent bronchopneumonia* which were almost invariably tuberculous, and probably had been such from the outset. I have also seen many cases of recurrent fever and cough in young people—sometimes without physical signs other than of seeming bronchitis; sometimes, if one times his examination fortunately, with areas of atelectasis—which I am sure are tuberculous and explain the numerous cases of healed and "latent" tuberculosis reported from the dead-house. Indeed, so far from feeling that I am called upon to establish the correctness of the suspicion of tuberculosis in cases in which this arises I am beginning to

feel that the burden of proof rests on the side of exclusion. When a case is far advanced, microscopic examination of the sputum showing lung-fiber or tubercle bacilli clinches the diagnosis. Unfortunately, these signs are not available early and the diagnosis is often exceedingly difficult and doubtful. The points on which more or less reliance may be placed are as follows:

1. The course of the fever, which is usually remittent in simple bronchopneumonia and often hectic or irregular in tuberculosis, though I have seen it sustainedly high and falling by crisis in cases undoubtedly tuberculous. Sometimes the temperature is of the inverse type.
2. The duration of the case, which is more prolonged in tuberculosis, passing into a chronic or subacute course, though death at times occurs early. These cases form the group of *rapid consumption* in young adults, though not rarely recovery or arrest takes place.
3. The antecedents, that is, the personal and family history of the patient. Heredity plays a marked influence; so, too, do causes affecting the health of the parents, even though they themselves do not become tuberculous. Bronchopneumonia following typhoid fever in a young adult is almost invariably tuberculous, and frequently does tuberculosis supervene upon the catarrhal pneumonia of measles and of influenza.
4. The physical signs are likely to be more pronounced in tuberculosis. There is some apical impairment. Crepitant and subcrepitant râles in the middle of a lung are more common. Sibilant râles in isolation are characteristic. As the case proceeds, the signs of breaking down become evident. The tuberculin test may be applied cautiously, by subcutaneous

injection of old tuberculin or of tuberculin residue; or by application of old tuberculin to the skin after the methods of von Pirquet or Moro. The conjunctival method of Calmette is not to be commended in view of the large possibility of accident, but the application may be made to the inner surface of the upper lip, on one side of the frenum.

In the early stages of tuberculous bronchopneumonia in infants all the signs are those of an ordinary bronchopneumonia, but these recede, and the only signs of consolidation left are metallic crepitant and subcrepitant râles. Hence a focus of subcrepitant or crepitant râles, localized and fixed, may be considered as evidence of tuberculous bronchopneumonia.

Associated with this stage of the disease is a dyspnea unaccompanied by distress or cyanosis, the dyspnea of ordinary bronchopneumonia being urgent and painful, but that of tuberculous consolidation leaving the child free from pain, and quite indifferent to the fact that its respirations are double or treble the normal frequency. Associated also with this stage is a rapid wasting, in spite of the absence of fever, vomiting, and diarrhea, and with the presence of a good appetite.

The extrapulmonary signs are the pale, dry, scaly skin; the long eyelashes; the exhausted appearance; the irregular bouts of fever; the enlargement to a very slight degree of the various lymphatic glands; the enlargement of the liver (enlargement of the spleen the writer regards as uncommon); the extreme susceptibility to cold, and, lastly, the localization of tubercle in the testis, or joints, or bones. G. Mouriquand (Gaz. des hôpitaux, Aug. 1, 1908).

**Influenza** is usually recognizable by the suddenness of the attack, by the great prostration, by the severe headache, by the cutaneous hyper-

esthesia and muscular pain, and by the disproportion between the great respiratory distress and the comparative paucity of physical signs. In cases of gradual onset and of extensive pulmonary involvement the diagnosis is much more difficult and depends upon the general association of symptoms. One point in favor of influenza in a given case would be the fact that a comparatively high fever—104° or 105° F.—in an adult is borne with little discomfort, the patient perhaps being scarcely conscious of fever. The character of the sputum, its sago-like appearance, is also significant. The discovery of the characteristic bacilli in the sputum clinches the diagnosis.

The writer recommends the following method of obtaining a pure bacterial culture in bronchopneumonia. He examines the patient's larynx in the usual way with a rather broad mirror, carefully sterilized, and avoiding all contact of the reflecting surface with the mouth. Previous gargling with dilute hydrogen peroxide solution is perhaps advisable. As soon as the larynx is in view, the patient is requested to cough slightly; often he does so spontaneously. Purulent matter is projected against the mirror, which is then withdrawn and supplies material for making cultures on the ordinary media. Where the patient is weak, the procedure can be used while he is recumbent, Rosenthal (Paris méd., Apr. 1, 1916).

The writers observed 9 fatal cases of bronchiolitis and bronchopneumonia, due to *B. influenza* of Pfeiffer, at a base hospital in France, in 1916-1917. Great dyspnea, marked cyanosis, rapid pulse, irregular temperature, the expectoration of large amounts of nummular sputum, and signs of a generalized bronchiolitis (with or without signs of consolidation), were characteristic of the disease. The diagnosis rested ultimately on the finding of Pfeiffer's bacillus as the predominating

micro-organism in the sputum. At necropsy this organism was grown in pure culture from the terminal bronchi, and no other organisms were seen here. Two cases showed acute endocarditis due to *B. influenza*, and in one of these the blood culture was also positive for the same organism. These cases apparently were sporadic. Malloch and Rhea (Quarterly Jour. of Med., Jan., 1921).

Examination of the sputum is of marked diagnostic importance in *necrotic influenzal pneumonia*. There occurs a sudden transformation from hemorrhagic to purulent expectoration, coupled with an abrupt increase in the amount and a diminished viscosity of the sputum. Upon microscopic examination elastic fibers are found to have appeared. Neutrophilic leucocytes with evidences of degeneration predominate among the cellular constituents, and there are also numerous sputum macrophages, filled with detritus. Recognition of the condition during life may depend entirely upon these sputum findings. E. Liebmann (Schweiz. med. Wochenschr., July 20, 1922).

**ETIOLOGY.**—Bronchopneumonia is sometimes an independent affection arising from "cold" or from direct irritation by smoke and noxious vapors and gases, and, in cases of such origin, it may likewise be associated with, or arise by extension from, inflammatory processes in the upper air passages. It may be caused by chloroform, and less often by ether, administered for surgical anesthesia in the presence of artificial light by combustion.

It may arise from purely local infection by agents recognized and not recognized, and probably not specific. It may occur in extension from bronchitis of any origin.

It is, however, usually met with as a complication or sequela of one of the infectious diseases, and especially of those of childhood. Even when it is



the only or most prominent manifestation of the existence of infection,—as, for example, in influenza or tuberculosis,—it is to be regarded as secondary.

It may be associated with, or follow, measles, scarlet fever, small-pox, whooping-cough, influenza, tuberculosis, erysipelas, dysentery, meningitis, and typhoid fever.

It also occurs from the aspiration of food (schluck-pneumonia, deglutition pneumonia, inspiration pneumonia) or infectious materials in cases of anesthesia or paralysis of the larynx, in coma of any origin, in malignant disease of the larynx and esophagus, following hemoptysis, following operations about the mouth and upper air passages, and in some cases through the inspiration of matters from a vomica or from a bronchiectatic cavity, or, in exceptional instances, from the rupture into the lung of a purulent collection in the pleura, liver, or elsewhere.

Tuberculous bronchopneumonia is the most common and most fatal form. Next in frequency is infectious bronchopneumonia associated with the diseases of childhood, which, according to distinguished pediatric authors, causes more deaths than do the fevers themselves. Rickets and diarrhea are likewise mentioned by authors among the predisposing causes affecting children. Thus, while the disease occurs at all ages, it is much more frequent in childhood and infancy. Old age may likewise be considered a factor in creating susceptibility to the disease, and it occurs in association with the various diseases and degenerative conditions incident to the decline of life. At all ages the disease is most prevalent among the poor.

It is, therefore, essentially a morbid process occurring in persons of lowered

or innately poor vital resistance, and in conditions which favor mechanically the entrance of infectious material into the bronchi.

Hardy found the mortality from bronchopneumonia 7.7 times as great in bottle-fed as in breast-fed children. Among 150 fatal cases, 15 followed measles, 8 meningitis, 5 otitis media, 3 pyemia, 2 administration of anesthetics, and 3 typhoid fever. Both lungs were affected in 132 cases, the right lung alone in 9, and the left alone in 9. Confluent or massive bronchopneumonia was present in 6 instances, and suppurative bronchopneumonia in 15. Acute fibrinous pleurisy was present in 15, and serous pleurisy in but 1. Empyema occurred in 16 cases.

*Postoperative* bronchopneumonia, commonest after abdominal operations, is by no means invariably an aspiration pneumonia. Thrombotic processes in vessels, resulting from inflammatory conditions, not infrequently exist previous to the operation, and when bronchopneumonia sets in 8 to 14 days after it, or even earlier, it can usually be ascribed to embolism with succeeding infarction. The condition nearly always develops on the right side, and occurs in individuals whose heart is unimpaired. Kohlmann (Fort. a. d. Geb. d. Röntgenstr., xxxii, 46, 1924).

**BACTERIOLOGY.**—Apart from the tubercle bacillus, the organisms most frequently found in bronchopneumonia are: *Micrococcus lanceolatus*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Staphylococcus albus*, *Bacillus pneumoniae* of Friedländer. In cases of diphtheria the Klebs-Löffler bacillus is frequently found, and in influenza Pfeiffer's and other organisms have been reported. It is rare for pure cultures to be found except in the case of the pneumococcus, which is most frequently associated with the pseudolobar type of the disease, the streptococcus being most common

in the lobar type. Mixed infection is the rule.

Transmissibility of bronchopneumonia emphasized, particularly as to children in hospitals. The pneumococcus is always present in their mouths, but is most copiously eliminated in the stools, so that transmission occurs chiefly through contamination of the hands. Cultural tests for droplet infection were seldom positive over 12 cm. ( $4\frac{1}{2}$  inches) from the children's mouth. Transmission is promoted by overcrowding. Isolation, asepsis and plenty of air-space should be insisted on. Ribadeau-Dumas and Fouët (Méd. infant., Mar., 1924).

**MORBID ANATOMY.**—The lungs exhibit inflammatory changes in the bronchial tubes, and areas of pulmonary consolidation, some of which are the result of collapse and some of vesicular inflammation. Collapse is caused as a result of the plugging of the bronchi.

The vesicular inflammation arises through hyperemia and edema in obstructed areas; by extension downward from the terminal bronchioles, or, as Balzer has shown, by extension laterally from the walls of inflamed bronchi.

All the coats of the bronchial tubes are swollen and thickened, and the reddened mucous membrane is usually, but not always, covered with a thick, tenacious, or even puriform mucus. Sometimes the mucus has become inspissated, marking out the course of the bronchi by yellow lines. Fibrinous concretions may be found. On section, especially in children, the cut extremities of the bronchi stand out from the surrounding tissue. Dilatations are observed, which in the larger tubes are commonly fusiform and cylindrical. In the smaller ones they are globular, and the terminal dilatations may attain

the size of a milletseed or hempseed. The pleural surface may be studded with such nodules, which yield a yellow fluid when punctured. They may, when distended by inspissated pus, strongly resemble tubercles. Pneumothorax sometimes arises from rupture of these distended globules into the pleural sac.

Pathologic study of bronchopneumonia in the aged, especially the nodular variety, which is much the commonest. The outstanding morbid feature in these cases is arterial obliteration, promoted by the well-known senile changes by which the arterial system is affected.

The lesions in nearly all the cases resembled septic pulmonary infarcts. In some instances they were actually triangular, like infarcts. In others this condition existed in 1 lung, while the other showed a more scattered nodular hepatization, but also with evidences of arterial obliteration. In a third group there were large lesions at the postero-inferior angle, and a large occluded artery was found immediately above. G. Roussy and R. Leroux (Ann. de méd., Mar., 1921).

Atelectasis, especially in children, is largely due to the obstruction of the bronchi by inspissated mucus. In early stages the collapsed area is still distensible by insufflation. This distinguishes it from lung-tissue filled with inflammatory products. Later, the distensibility may be lost. An atelectatic area is generally distinguishable from one of infiltration by being sunk below the level of the surrounding tissue, by its glistening, smooth section, and by the fact that, when the collapse occurs at the surface of the lung, the pleura shows no sign of exudation and still maintains its transparency. Such areas are harder and resist pressure more than inflamed portions of the lung, and when scattered thickly throughout the

organ may give to the finger the sensation of shot-grains.

On scraping or pressure a thick, white fluid escapes, which under the microscope contains proliferated epithelium and leucocytes. Fibrinous exudation is never marked and may be entirely absent from many areas. When vesicular inflammation has occurred in extension from the bronchi the nodules may be microscopic or may reach the size of a hempseed. In early stages they may be dark red, but usually they are of a finely granular, yellowish or dull-white appearance, fading insensibly into the surrounding tissue. If in a collapsed area, however, they stand out rather prominently from a bluish, purplish, or even black background. Abscess or gangrene is sometimes present. Sometimes inflammatory changes may be found scattered through a collapsed and congested part.

Hemorrhagic extravasations are often seen. They are mostly subpleural and petechial, but may be more extensive. Emphysema is almost constantly found; mainly in the upper lobes, especially along their anterior margins. Interlobular emphysema is not uncommon in fatal cases of whooping-cough at early ages.

Resolution is often complete; sometimes dilatation of the bronchi, with some condensation of surrounding pulmonary tissue, persists for a long time, perhaps indefinitely. Chronic induration of the lungs following acute bronchopneumonia is not very rare, if one may judge by clinical observation. In debilitated subjects, especially in children the subjects of scrofula or rickets, caseation and ulceration, not to be distinguished from tuberculosis, supervene. Tubercle bacilli may be found in the neighborhood, but whether of late ap-

pearance, or whether the process has been tuberculous from the first, it is not always easy to determine.

Pleuritis is a frequent complication of bronchopneumonia, but effusion of any extent is not common. Over collapsed portions the pleura is not inflamed, and this may aid in the diagnosis between atelectasis and pneumonia. The bronchial glands are swollen, sometimes distinctly hyperemic. In rare cases they are unaffected. Sometimes they show cheesy spots or calcified nodules, usually in connection with tuberculosis of the lung.

The right side of the heart is usually dilated, and in young infants there may be in consequence persistence of the openings of the foramen ovale and ductus arteriosus. Thrombosis of the pulmonary artery and pericarditis are among the occasional complications.

Other organs show, for the most part, only the results of venous congestion. Edema and congestion of the brain are common in fatal cases. Actual meningitis, however, is rare. Congestion of the liver, the stomach, and intestines is frequent, and erosions may be found in the large intestine. The kidneys are usually congested. Concretions of urates are often found in the straight tubules of the pyramids. Anasarca and ascites are infrequent.

**TREATMENT.**—While to some extent dependent upon the exciting cause of the pathological process in the individual case, and subject to modification according to age, sex, personal characteristics, environment, and so forth, the general lines of treatment in cases of bronchopneumonia are very much alike in all cases.

In the acute form of the disease rest is necessary, and, if the process be severe, rest in bed. Sufficient ventila-

tion without exposure of the patient to draft is a necessity. In general, the temperature of the sick-room should be kept as near 60° F. as possible. When the patient is aged, or in the case of capillary bronchitis in children, a higher temperature, even to 80° F., is sometimes desirable. In capillary bronchitis, too, the air of the room should be kept moist by the evaporation of water, on which aromatic or terebinthinate substances—**eucalyptol**, **menthol**, **benzoin** (preferably the compound tincture), etc.—may be thrown, so that their vapors may be pleasantly and equably diffused. Or, a “**croup-tent**” may be placed about the patient’s bed, and the air within it be moistened and medicated.

In many cases, the **open air** is better than any room. The roofwards of hospitals show an exceptionally low mortality. Especially is the open air of roof, porch, or tent desirable in cases of tuberculosis, and hardly less so in influenza. The patient’s head and body should be kept warm, however, by coverings adapted to the weather, and if necessary by hot-water bottles in the bed.

**Hot flaxseed poultices** applied over the affected area, or, when the process is widespread, over the entire chest, front and back (jacket poultice), are of great service. The poultice should be well made by slowly stirring boiling water into successive portions of flaxseedmeal, and the mixture should then be spread between two layers of cheesecloth. Oiled silk should be applied over the poultice, and the whole kept in place neatly by pins or bandage. Well made, properly applied, the poultice should retain its heat from four to six hours. From two to three poultices are to be applied during the day, and

“at bedtime” the skin is to be well dried and sponged with alcohol and alum, and the chest enveloped in a jacket of lambs’ wool. The following day and the third day, if necessary, the poultices are reapplied, the lambs’ wool being again substituted at night. It is rarely advisable to continue poulticing longer than this. In some cases poulticing may be preceded by counterirritation. The best method of counterirritation is by means of a mild **mustard plaster**, made with the addition of glycerin and white of egg. This can be retained in position for an hour or two without bad effect. In children it is better to rub the chest with amber oil night and morning, or a modification of St. John Long’s liniment may be used; for example:—

<b>R</b> <i>Amber oil,</i>	
<i>Oil of turpentine,</i>	
<i>Oil of eucalyptus,</i>	
<i>Oil of wintergreen,</i>	
<i>of each</i> .....	½ fl. oz. (15 c.c.).
<i>Linseed oil</i> .....	1 fl. dr. (4 c.c.).
<i>Olive oil</i> .....	½ fl. oz. (15 c.c.).
<i>Vinegar</i> .....	1 fl. oz. (30 c.c.).
<i>Yolk of 1 egg.</i>	
<i>Water, sufficient to</i>	
<i>make</i> .....	¾ pt. (240 c.c.).

Sometimes the lambs’ wool or cotton jacket may be applied immediately, or following upon the counterirritation without the use of poultices. Considerable pain in the chest, widespread, or massive, consolidation or blocking of the air-vesicles constitute the indication for the use of poultices. In tuberculous cases, and when for any reason poulticing cannot be properly carried out, **dry heat** by means of hot-water bag, salt-bag, electric heating pad, etc., or **moist heat** by hot compresses may be substituted. The **application of ice to the chest** is strongly urged by some writers, cases of both croup-

ous and catarrhal pneumonia being included in their reports, which are exceedingly favorable. I do not employ the ice-pack in bronchopneumonia; but in tuberculous cases when the temperature exceeds 100° an ice-bag or a cold precordial coil should be applied over the cardiac area.

According to Kerley, **steam inhalation with creosote** (10 drops—0.6 c.c.—to 1 quart—960 c.c.—of water) under a croup tent, for thirty minutes every three hours, admitting fresh air every ten minutes, is useful. **Mustard applications** make the best counterirritation. The plaster is to be made with 1 part of mustard to 2 parts of flour, and applied for 10 to 15 minutes once in 6 to 8 hours. Later applications should be weaker. They are especially effective at the onset, as are **mustard baths**, especially in cases with marked prostration.

Herzfeld has also strongly recommended **mustard** as a counterirritant in bronchopneumonia in infants and children. The method is as follows: 250 c.c. (half a pint) each of water and alcohol are mixed in a large bowl; to this are added from 25 to 50 c.c. ( $\frac{1}{4}$  to  $1\frac{1}{2}$  ounces), according to the severity of the case, of freshly prepared spirit of mustard. The latter is prepared according to the German Pharmacopeia: Oil of mustard, 1 part; pure alcohol, 49 parts. A large piece of flannel is moistened with the mixture and wrapped around the child from the neck to the knees. The child is then enveloped in a dry sheet and the pack left on until the skin is a bright red, usually in 15 to 30 minutes. The child is then taken out and wrapped and left for another half-hour in a pack wet with 1 part alcohol and 2 parts water. At the end of this time the child is wrapped in a dry sheet. Usually one pack causes marked improvement, but relapses are frequent, and it may need renewal. Once in 24 hours is enough unless the indications are unavoidable. The physician should apply the first pack himself.

The writer recommends **mustard poultices**, applied just long enough to redden the skin, several times a day and for several days. **Dry or wet cupping** is serviceable, but blistering

is to be avoided. **Hot, dry cloths** are also useful. For sedative purposes **baths** at 38° C. lasting 20 minutes are advised, though contraindicated in heart weakness and extreme dyspnea. P. Lassablière (*La médecine*, Aug., 1921).

Good results in bronchopneumonia are obtained with **ammonium chloride**, 5 grains (0.3 Gm.) every 3 hours, and **potassium iodide** in the same dose every 6 hours, together with **free catharsis**. In influenzal cases the **throat and nares** should be frequently **sprayed**, during the early part of the illness, with some hot antiseptic solution. **Hot sponge baths** are given night and morning, and oftener if indicated. Stimulation is adjusted to the actual condition of the heart, **tincture of digitalis** in alternation with **strychnine** being generally used. For cough, **codeine** or **diacetylmorphine** may be added to the ammonium chloride if absolutely necessary, but never morphine during the stage of active consolidation. For other sedative purposes, the writer uses **bromides** freely, and as hypnotics, **barbital** or **trional**. C. S. Cole (*Med. Rec.*, Nov. 19, 1921).

In influenzal cases with much congestion and bronchitis, **counterirritation** may be usefully continued for a time. In cases with definite areas of bronchopneumonia and absence of bronchitis or edema, **opium** may be used the first 2 or 3 nights, but in diffuse cases with general bronchiolitis it should be withheld. If  $\frac{1}{100}$  grain (0.0006 Gm.) of **atropine** does not give the desired relief in cases with much bronchial secretion it may be increased up to  $\frac{1}{30}$  grain (0.002 Gm.) and repeated 4 hourly for a few doses. But in the grave cyanotic influenzal cases with much dyspnea the author finds most helpful **ammonium carbonate**, 10 grains (0.6 Gm.) in a tea-cupful of milk every hour for 6 doses, repeating the course if necessary after omitting the drug for a few hours. **Pituitrin**, 16 minims (1 c.c.), may be injected deeply into the muscles for vasomotor failure. The heart is best

helped by food and oxygen. The best food for it is **sugar**, which can be given from the first as cane sugar, milk sugar, or honey. Intravenous 10 per cent. **glucose injections** are perhaps most valuable when circulatory failure has commenced. In the severe influenzal cases with edematous lungs and blocked bronchioles, **oxygen** can be given **subcutaneously**. W. H. Wynn (Lancet, Sept. 2, 1922).

For restlessness **pantopon** is the most effectual opiate, its content of narcotine especially reducing its depressing action on the medulla. In extreme delirium, however, where unduly large doses of opiates would be required, **hyoscine** is preferable. In a case of bronchopneumonia with violent delirium, restlessness continuing even after  $\frac{1}{3}$  grain (0.02 Gm.) of pantopon, so that 5 nurses were required to hold the woman in bed, an injection of hyoscine brought complete relaxation. G. L. Waldbott (Med. Jour. and Rec., Dec. 3, 1924).

**Sponging** the entire body twice daily with **tepid water** and **aromatics** or **alcohol** adds greatly to the comfort of the patient. Should the temperature be high, cool sponging, the cold pack, constant cool compresses, or the bath may be used. There must not, however, be any sudden shock in the latter case. The child should be plunged in water at 95° F., gradually reduced to 80° during the first bath. Friction should be used and the duration of the bath be from eight to ten minutes. Subsequent baths with successively lower initial temperatures not falling below 80°, and final temperatures not falling below 70°, may be given at intervals of about four hours whenever the temperature exceeds 104° F. Sometimes, especially with delicate or much depressed children, or the aged and feeble, **hot applications** (sponging, packing, or plunging, according to circum-

stances, of which the age and general reaction of the patient are the most important) are to be preferred. The effect upon general comfort as well as upon temperature must be considered. In cases of meningitis or with severe cerebral symptoms, an **ice-cap** should be applied to the head. Antipyretic drugs should never be given.

**Hydrotherapy** is useful in some cases at least, especially in children. A **sponge bath** at 90° F., later reduced to 80° F., followed by gentle toweling of the surface, to secure full reaction, often acts well. A high temperature calls for a **cold pack**, a sheet doubled and wrung out of water at 80° F. being wrapped evenly about the patient and allowed to remain  $\frac{1}{2}$  to 1 hour. J. M. Anders (Jour. Amer. Med. Assoc., July 26, 1924).

In acute bronchopneumonia complicating chronic pulmonary tuberculosis, a **cold application** may be made **over the heart**, as stated, whenever the temperature shows a tendency to exceed 100° F. The application should be continuous until the temperature declines, and should be repeated according to necessity. Should this fail to bring the temperature to or below 100° F., **nitrogen monoxide**, about 8 gallons daily, should be given **by inhalation**. As the rise in temperature is usually postmeridian, the inhalation should be given in the forenoon, 4 gallons being administered at about 9 o'clock and 4 at about 11 o'clock. This will also conduce to sleep at night.

**Food** should be given as in fevers generally, in small quantities, at intervals of two or three hours, and should consist of easily assimilable and concentrated nutriment, pancreatized milk, broths, egg-albumin, soft-boiled eggs, and the like. Children, the aged, and

tuberculous patients are usually benefited by **alcohol** in small quantities, given with the food. The patient should be encouraged to drink water freely, so as to keep up to, or, better, beyond, normal the quantity of urine excreted, and it is usually well to give a mild alkaline diuretic, as solution of **potassium citrate** or solution of **ammonium acetate**.

The **diet** should consist of semi-solid or liquid foods. **Forcing of fluids** is deemed of great importance. Glass partitions are used to separate the children into groups not exceeding 2 or 3 patients, both to obviate over-crowding and to provide plenty of **fresh air**. Cool, but not icy cold air is used to ventilate the rooms. When the temperature rises above 103.5° F., **sponge baths** are given every 3 hours, together with an **ice-bag to the head** and a **hot water bottle to the feet**. Both **digitalis** and **camphor** are used throughout the period of high temperature. The former is given in the tincture, to the amount of 1 drop for each pound of body-weight each 48 hours, reduced  $\frac{1}{2}$  when the heart has become digitalized. If prompt stimulation is indicated,  $\frac{1}{2}$  grain (0.03 Gm.) doses of **caffeine sodio-benzoate** hypodermically are used to support the patient until the action of **digitalis** sets in. In cases in which high temperature is combined with pronounced delirium and toxemia, **whisky** is valuable when given in amounts sufficient for a full physiologic effect. For extreme toxemia, daily cleansing of the intestinal tract by **rectal irrigation with sodium bicarbonate solution**, coupled with mild **purgation**, proves helpful. Moffett (Arch. of Ped., Nov., 1924).

If there is any tendency to constipation, or any failure of daily action of the bowel, **calomel**, **alkaline laxatives**, **glycerin suppositories**, or **enemata** should be employed according to circumstances. It is advisable to

begin treatment with the administration of **castor oil** (perhaps with an equal quantity of **aromatic syrup of rhubarb** to make it palatable) or of **calomel** in divided doses.

Injection of **ether** in bronchopneumonia to combat the infection advised. As a rule, injection of 1 c.c. (16 minims) every four hours is sufficient, sometimes even only morning and night. Frequently a single injection proves effective, especially when administered early in the course of the disease. In addition, **heart tonics** and **counterirritation with mustard** are employed. No untoward effects were noted in over 200 injections. Lassalle (Arch. de méd. des enfants, July, 1920).

Case of early bronchopneumonia in measles, somewhat suggestive of tuberculosis. **Artificial pneumothorax** was instituted, a series of 5 insufflations being given. After the second, the temperature dropped, and soon remained permanently at normal, complete recovery following in 2 weeks. L. Bernard (Bull. Soc. méd. des hôp. de Paris, Dec. 6, 1923).

Subcutaneous **injections of ether vapor** in a menstruum of **oxygen gas** favored in bronchopneumonia and other serious lung disturbances of children, as well as in whooping-cough. Pure ether hypodermically is similarly beneficial, but the resulting pain and other possible untoward local effects render the administration in oxygen more desirable, the oxygen itself, moreover, acting favorably. The oxygen is passed through a tube containing ether, which is vaporized and carried along by the oxygen to the extent of 2 c.c. of ether per 100 c.c. of oxygen. Gentle application of heat with the hand or warm water hastens the vaporization. The dose of ether is 2 c.c. in children of 1 to 2 years and 1 c.c. or less in those below 1 year. In acute lung disorders, an injection is given daily at first, then on alternate days, and finally the oxygen is used alone. J. Jarricot (Ped. españ., Oct. 31, 1924).

**Case** of a girl of 8 who developed bronchopneumonia in the course of whooping cough. It persisted extremely grave for 5 months and then subsided completely. The child required **oxygen** daily for more than 2 months. Recurring spinal pains were relieved by **reclining on a hard bed**. Vomiting and anorexia hampered nutrition, but on milk, soups, lightly alcoholized fluids, eggs, etc., strength was regained. Garragan (Arch. Latina-Amer. de Pediatria, May-June, 1918).

The general medication should be adjusted to the individual case, and modified from time to time according to circumstances. There are many available agents, among which intelligent choice is to be made. **Quinine** given in large doses, especially the double hydrochloride of quinine and urea injected intramuscularly, is of great service in croupous pneumonia, and hardly less so in bronchopneumonia.

In the writer's experience the following method has given good results: A 25 to 50 per cent. solution of the quinine and urea in sterile hot water is injected deeply into a muscle, through skin previously painted with tincture of iodine. Care is taken to empty the syringe before withdrawal, to avoid dropping solution upon the pierced skin, and the point of puncture is sealed with collodion or iodoform-collodion. For a robust adult the initial injection is 1 Gm. (15 grains) to 1.6 Gm. (25 grains); for aged persons 0.6 Gm. (10 grains); for children about 0.032 to 0.065 Gm. ( $\frac{1}{2}$  to 1 grain) for each year of age, taking the vigor of the child and the severity of the case into consideration. The dose is repeated every three or four hours so long as the temperature shows a tendency to remain above

102° F., unless cinchonism develops. Sometimes only a single injection is made. Sometimes several injections are made daily for two or three days. The entire result must be considered. The drug may be given by the mouth when injection is not practicable. At the outset in the aged, and in feeble children, **strychnine** should be given in doses of about  $\frac{1}{120}$  grain (0.0005 Gm.) to  $\frac{1}{250}$  grain (0.0002 Gm.), repeated at intervals of from one to six hours, according to age and effect. It is not well to make a profound impression with the drug, or the patient's recuperative force will be exhausted. A gentle and continuous support of the vital powers is the object aimed at. For emergencies **strychnine** may be given hypodermically in doses to suit the occasion. Should cardiac or respiratory debility become alarming, **strychnine** should be supplemented by **atropine** [ $\frac{1}{2000}$  to  $\frac{1}{200}$  grain (0.00003 to 0.0003 Gm.), by skin or by mouth, every hour or at longer intervals, according to age and condition] or by **camphor**, which in children usually acts effectively when given as spirit of camphor by the mouth, in appropriate dosage: from 1 to 10 drops (0.06 to 0.6 c.c.); to an infant,  $\frac{1}{4}$  drop (0.015 c.c.) in hot water. To an adult, **camphor** should be given hypodermically, dissolved in sterilized olive oil, 1 to 10; one, two, or three syringefuls of 20 to 30 minims each may be given, as needed, or the solvent may be half ether and half oil. Hypodermic injections of **ether**, with or without **camphor**, are sometimes useful. **Cocaine hydrochloride** [for an adult,  $\frac{1}{2}$  grain (0.03 Gm.) hypodermically *p.r.u.*] is useful to relieve dyspnea and to sustain blood-pressure.

When quinine injections are used



**cocaine** should be given conjointly. The indication is a tendency for systolic blood-pressure measured in millimeters of mercury to fall below pulse rate measured in beats per minute. In a grave emergency, intravenous injection of a sterile solution of the **adrenal principle** might be serviceable. To children **alternate hot and cold douches** may be applied. The **ammonium preparations** are useful in nearly all cases. The aromatic spirit of ammonia, ammonium carbonate, ammonium chloride, or ammonium salicylate may be chosen. A good formula for an adult consists of:—

<i>R</i> Ammonium chloride .....	10 grs. (0.6 Gm.).
Ammonium carbonate .....	5 grs. (0.3 Gm.).
Fluidextract of coca .....	1 fl. dr. (4 c.c.).
Spirit of nitrous ether .....	20 min. (1.25 c.c.).
"Essence of pepsin" (neutralized) .....	1 fl. dr. (4 c.c.).
Water, or Solution of ammonium acetate, sufficient to make .....	½ fl. oz. (15 c.c.).

Dose: Tablespoonful (½ fluidounce—15 c.c.) every two, three, or four hours. The mixture will be turbid, and it may be necessary to "shake."

The coca in this formula, while it is useful as a heart tonic and diuretic, is used primarily merely to disguise the ammonium taste, and the pepsin preparation helps the stomach to bear the medicine. If pleurisy exists, **ammonium salicylate** may be added to this mixture. Another useful method of giving **ammonium carbonate** is to dissolve 5 or 10 grains (0.3 to 0.6 Gm.) in a dessertspoonful of **liquor ammonii acetatis**, and put this dose with

15 drops (0.9 c.c.) of **glycerin** and a dram or two (4 to 8 c.c.) of **sherry wine** in a wineglassful of cracked ice. Sometimes **egg-albumin** may be added. The whole can be swallowed at a gulp, and will often be retained without disturbance of the stomach when the drug cannot otherwise be given.

**Opium** need not be given except there be urgent indication to relieve pain or quiet excessive unproductive cough. It should then be used with circumspection. **Codeine** is usually the best preparation, but, if preferred, the **deodorized tincture of opium** or the **camphorated tincture of opium** may be added to the **aromatic spirit of ammonia** or other ammonium preparation employed. With children, **paregoric** is usually the best form in which to give opium.

In cases of continued weakness of the heart not sufficiently urgent to call for the hypodermic use of **camphor**, **tincture of digitalis** or Merck's German **digitalin** or other trustworthy **digitalis** preparation may be used in such doses and such manner as will produce the effect desired. **Caffeine** may also be used for more immediate effect, as **digitalis** is slow, but not always sure. When there is a tendency to edema of lungs and skin, **belladonna** or **atropine** may be associated or alternated with the **digitalis** or **caffeine**. **Strophanthus** is available sometimes, when **digitalis** fails. In tuberculous cases, especially those with high fever, **digitalis** may be employed in fairly large doses, as urged by Beddoes, and this use of it sometimes seems to be followed by the happiest results. From 20 to 30 drops (1.2 to 1.8 c.c.) of a good tincture may be given to an adult from three to six

times a day, until the pulse is reduced to 60 beats per minute; after which sufficient is given, the stomach permitting, to keep the pulse rate in the neighborhood of 70.

In children, and especially if the symptoms be those of suffocative catarrh, it is well to cause occasional emesis, for which purpose **syrup of ipecacuanha**, **alum in syrup of ipecacuanha** or in honey, or, if these fail, **apomorphine** may be employed. **Turpeth mineral** has been commended, but I have never used it. Following the emesis there is sometimes much prostration. I have found the inhalation of **amyl nitrite**, cautiously administered, of great service at this time, and also when suffocation cannot be relieved by emesis. In such cases, too, some more active expectorant than the **ammonium preparations** may be continuously necessary, and **syrup of senega**, **squill**, or **ipecacuanha** may be used. In mild cases a useful mixture is made with 5 to 10 minims (0.3 to 0.6 c.c.) each of **syrup of ipecacuanha**, **aromatic spirit of ammonia**, and **paregoric**, in water, which may be given every second or third hour.

The bronchopneumonic child's position in bed with shoulders raised should be frequently changed. In mild cases a **warm bath** twice a day, rubbing the arms and legs well, is soothing; in the severer cases the bath water must be heated from 37° to 40° or 41° C. by pouring in more hot water, rubbing the limbs, and keeping the child from six to ten minutes in the bath.

Steam from boiling water generally will keep the cough loose, but if an expectorant is necessary the writer gives 10 drops (0.6 c.c.) three times a day of a mixture of equal parts of **anisated solution of ammonia** and **fluidextract of senega**, in sweetened water. Heart tonics are more often

needed than expectorants, and he prefers for infants 5 Gm. (1¼ drams) from three to five times a day of a 0.5 per cent. solution of **caffeine sodium benzoate**, doubling the dose for children of 2 to 4. **Camphorated oil** in subcutaneous injection can be given from two to six times a day at need. When rachitis impedes recovery, **phosphorus-codliver oil** may aid the cure. Feer (Jour. Amer. Med. Assoc., from Med. Klinik, April 21, 1912).

**Intravenous injections of mercuriochrome-220 soluble** found of great value in the pneumonias of infants and children. The disease is sometimes shortened and often abruptly terminated. Of the cases treated, 7 had bronchopneumonia and 5 lobar pneumonia. Two patients died. In 1, death was inevitable before the drug was given. The other, with cyanosis of unknown origin previously present for several years, showed definite improvement at first but later failed to respond to treatment. In 7 cases, but 1 injection proved sufficient; 3 required 2 injections, and 2, 3 injections. The average dose was 0.005 Gm. per kilogram of body-weight, given in a 1 per cent. solution. In the preparation of this solution, the drug is simply dissolved in distilled water and the solution filtered. It is self-sterilizing and should not be heated.

Usually the systemic reaction is mild. In a few hours after injection there is often a rise of 1 or 2 degrees in temperature. The urine is often colored pale pink by the drug, and sometimes the feces are colored red. The very marked clinical improvement usually seen a few hours after the injection sometimes occurs without any marked change in temperature or pulse rate.

In a case of bronchopneumonia in a child of 5½ years, severe, foul diarrhea had developed in the 4th week, and on the 38th day she was in a desperate condition, with 5 areas of lung consolidation, ears discharging profusely, many skin abscesses, and cyanosis. **Mercurochrome** being given, the temperature fell as if by crisis, and she began a rapid and uninterrupted recovery.

From 2 to 4 hours after the injection a rapid fall in temperature usually occurs; occasionally, when not so abrupt, the fall resembles a very sudden lysis. The most striking effects, however, are seen in the patient's general appearance; in a few hours the child appears comfortable and quiet, as after the crisis in pneumonia.

Experiments showed that in a dilution even greater than that existing in the blood when the drug is given intravenously in the dose referred to, it will kill the *Streptococcus hemolyticus* in defibrinated blood in 1 hour. W. T. Freeman and L. D. Hoppe (Amer. Jour. Dis. of Childr., Sept., 1924).

In influenza, **salicin**, **sodium benzoate**, and **cinchonidine salicylate** are useful, and are to be associated with or substituted for other drugs mentioned.

In tuberculosis, **salicin** and the **guaiacol salts** (carbonate, cinnamate, and salicylate) are to be employed, or, if the stomach will bear it, **creosote** may be given. **Creosote carbonate** may often be given in large doses when creosote cannot be taken. Creosote carbonate is also useful in many non-tuberculous cases, especially when there is much cough and somewhat scanty expectorations. The best way to administer the drug is in hot milk. The dose [1 to 5 drops (0.06 to 0.3 c.c.) for a child, 5 to 15 drops (0.3 to 0.9 c.c.) for an adult, every two to six hours] may be floated on a tablespoonful of the milk and thus swallowed, after which from 2 to 6 ounces (60 to 180 c.c.) of unmedicated milk should be sipped slowly. It is usually well to alternate the creosote preparation with **salicin**, the **ammonium salts**, **ippecac**, **digitalis**, **belladonna**, or **strychnine**, as the case may be, when any of these drugs is indicated.

As recovery takes place, the medica-

tion, whatever it may have been, should be gradually withdrawn. Should resolution be sluggish, it is well to give **ammonium iodide**, preferably in a vehicle containing **pepsin**, and followed by a large draught of water. The dose should be small at first, 5 grains (0.3 Gm.) for an adult, and gradually increased. The application of **hot poultices** for a few days is again likely to be useful.

When recovery is unduly delayed the application over the affected areas of **mercurial ointment**, or of **iodine in lanolin** (20 grains—1.3 Gm.— to the ounce—30 Gm.), or in liquid **saponified petrolatum**, often seems to hasten it. The **iodine ointment** should be applied a few drops at a time, and well rubbed in until a dram (4 Gm.) or more has been taken up by the skin. A gauze dressing covered by oiled silk or rubber tissue should then be placed over the treated area. **Calomel** in small, frequently repeated doses for two or three days, just avoiding salivation, is not rarely useful at this time.

Should there be suppression of urine, bloody urine, or albuminuria, it is well to suspend all medication except some bland **alkaline diuretic**, and **take blood**, either from the arm or by **wet cups over the kidneys**, after which **warm** (100° to 104° F.) **physiological saline solution** should be introduced slowly, either by a vein or under the skin. **High irrigation of the colon with hot physiological saline solution** (110° F.) may temporarily substitute the venous or subcutaneous infusion. The Murphy method of **continuous enteroclysis** may be employed in suitable cases. When the condition of the patient is markedly septic or toxemic, as shown by muttering

delirium and general depression, the same measures should be used.

**Leeching** back of the ears may be the best method of depletion in cerebral cases. When the chief difficulty seems to be in the circulation, if one can be sure that the obstacle to circulation is not merely the weakness of the heart, but that the latter is simply an indication of peripheral difficulty, bloodletting by **wet cupping** over the chest or even by **venesection** is justifiable, and the introduction of **saline solution** may usefully follow. Sometimes the use of **nitroglycerin** internally suffices.

When the respiratory obstruction seems to be great, as shown by cyanosis, dyspnea, rapidity of breathing, short, hacking, incessant, unproductive cough, there is no measure so useful as the **inhalation of oxygen**. At first this must be as nearly continuous as possible. As improvement takes place, the intervals and duration of inhalations are modified accordingly. It is especially in children, in the aged, in cases following the exanthemata, and in septic cases generally that I have seen oxygen save life. If resort to it be too long delayed, or its administration be economical or timid, no good result is to be anticipated.

The mortality in pneumonia should be reduced to a low rate by proper **oxygen** therapy and medicinal heart support. It has been shown that there is a varying degree of anoxemia almost from the start, which oxygen relieves at once. Early administration of oxygen is important because the effect of oxygen deficiency on the nerve centers and tissues develops insidiously, and once started, the damage leads to progressive deterioration of the vital functions. For the same reasons, the oxygen should be continued until all signs of deficient oxidation are past. Small doses of **digitalis** from the outset are advantageous. For collapse with small thready

pulse, **adrenalin**, given slowly, is useful, with **atropine sulphate** as respiratory stimulant. R. S. Rowland (Jour. Mich. State Med. Soc., Jan., 1925).

Convalescence must be skillfully managed to avoid the development of chronic bronchopneumonia, or the supervention of tuberculosis in non-tuberculous cases. **Food, fresh air, cold-water bathing, and friction of the skin** with perhaps, in some cases, roborant medication by means of **iron, arsenic, calcium glycerophosphate**, and the like, and regulated **pulmonary gymnastics** meet the indications. In some cases, especially when scrofula exists or tuberculosis is suspected, the continuance of **creosote** or the administration of **guaiacol cinnamate** is necessary.

Chronic bronchopneumonia calls for good general **hygiene** and **nutrition**, the application of a series of small **fly-blisters over the chest** (about one inch square; one at a time; applied over a new area each time; with intervals of three or four days between applications), and systematic expansion of the chest by **inhalation of compressed air** or other efficient means. Internally, iodine compounds are to be given. Pills or capsules of **iodoform**, or of iodoform and iron, or of iodoform, **iron**, and **arsenic** may be alternated with **ammonium iodide** or **syrup of hydriodic acid**. Small doses are to be given at first, and gradually increased to the point of tolerance. **Strychnine** and **calcium glycerophosphate** are useful tonics, and may be alternated with the doses of **iodoform**.

If the cases prove rebellious to any of the lines of treatment described above, a **sea-voyage** should be recommended, and, this failing, **change of residence**—temporary or permanent—

to a cold, dry region, preferably at a considerable altitude, in the case of one young and robust; to a warm, but dry and equable region in the case of the aged.

Various **serums** and **vaccines** have been employed in bronchopneumonia, in some instances apparently with good results.

Eight adults and 22 children treated by massive hypodermic or intramuscular injection, repeated daily for 2 or 3 days, of **polyvalent antipneumococcic serum**, in conjunction with daily ascending injections of **pneumostreptococcic vaccine**, continued after cessation of the serum treatment. The treatment was found to cause a marked increase of the already existing leucocytosis, and the leucocytes remained at a high level as long as the disease focus was active. When vaccines were used alone, there was usually an initial leucopenia and a late leucocytosis. In this series of 30 cases there were 5 deaths. D'Oelsnitz and Colle (Bull. et mém. de la Soc. méd. des hôp. de Paris, June 1, 1922).

A dramatic defervescence follows injection of a suitable dose of **vaccine** in pneumonia or influenzal bronchopneumonia within 24 hours of its onset. In the latter condition, the author uses a triple vaccine containing equal numbers of pneumococci, streptococci, and influenza bacilli, and to an adult administers 100 millions of each organism; to a child of 12 to 14 years, 40 to 50 millions, and to a child of 2 or 3 years, 10 to 20 millions. If given on the first day, in the majority of cases the temperature falls to normal on the following day and no further treatment is required. The dose can be repeated every 24 hours until the temperature has fallen. Influenzal bronchopneumonia during an epidemic period resembles lobar pneumonia in that an active **stock vaccine** can be prepared for immediate use, whereas with other bronchopneumonias some time is lost in discovering the

nature of the infection. Out of 51 patients injected within the first two days all recovered but 1, who, after defervescence in 36 hours, died on the ninth day of pulmonary embolism. Out of 56 patients first injected on the third, fourth, or fifth days, 47 recovered. W. H. Wynn (Lancet, Sept. 2, 1922).

**Antipneumococcic serum by nasal or rectal instillation** used with benefit in pneumococcic infections in children, including bronchopneumonia, bronchitis, nasopharyngeal catarrh, otitis, and protracted pneumococcic infection suggesting tuberculosis. These methods proved as effective as subcutaneous injections, and are easily used where such injections, or the intramuscular or intravenous routes, are impracticable. The dosage is 15 drops of serum instilled into each nostril 4 or 5 times a day, or 5 or 6 drops at hourly intervals. In grave cases the rectal instillations of 10 to 15 c.c. of serum are given in addition. Where there are intranasal foci the serum is thought to act specifically upon the bacteria locally present. G. Blechmann (Bull. Soc. de péd. de Paris, Feb.-Mar., 1924).

A **polyvalent vaccine** of the pneumococcus, enterococcus, staphylococcus and tetragenus organism proved of value in bronchopneumonia in infants, 36 out of 41 cases recovering under this treatment. It was particularly effective in cases of primary pneumonia, less so in the pneumonias secondary to measles, whooping-cough or diphtheria. E. Weill and A. Dufourt (C. r. Soc. de biol., Aug. 12, 1924).

The mortality of both bronchopneumonia and lobar pneumonia in children can be greatly reduced by addition of **chicken blood** or **serum** to the usual measures. There exists in normal chicken serum a protective substance against the pneumococcus of Types I, II and III, and the chicken is tolerant to large doses of pneumococci injected intraperitoneally. In treatment, the duration of the illness before injection, the dosage, and the age of the serum used are vital factors.

Among 41 cases treated with chicken

blood or serum the mortality was 12.2 per cent., while among 22 cases not receiving it the mortality was 36.3 per cent. Among the treated cases, the bronchopneumonia patients required an average of 2.81 days for the temperature, 1.83 for the pulse, and 2.51 for the respiration to reach normal, while in the case of those not receiving chicken blood or serum the corresponding average periods were 11, 9.6, and 10.4 days. Closely similar results were seen in the lobar pneumonia cases.

The chicken blood was collected in  $\frac{1}{2}$  gallon jars containing a known quantity of sodium citrate solution. Upon withdrawal of the serum, the citrate was removed with calcium and the serum then run through Berkefeld filters. The sterility of the serum having been proven by culture and injection into animals, trikresol was added as preservative and the serum divided among 100 c.c. rubber-capped containers. H. C. Berger and J. G. Montgomery (Arch. of Int. Med., Dec., 1924).

Good results in bronchopneumonia or pneumonia in children from injections of a *diplococcus vaccine*, given daily or on alternate days. In infants below 1 year of age the mortality was but 12 per cent. Favorable effects also witnessed in diplococcic pneumonia complicating pertussis and in empyema. E. M. Mondini (Pediatrics, May 15, 1925).

SOLOMON SOLIS-COHEN,  
Philadelphia.

## BRONCHOSPIROCHETOSIS.

—This disorder, also known as **bronchial or bronchopulmonary spirochetosis**, or **spirochetosis bronchialis**, was first described by Castellani in 1906, and defined as "a peculiar form of bronchitis characterized by the presence of enormous numbers of spirochetes in the expectoration." At first it was reported from India, Ceylon, the Philippines, and the West Indies, but during the World War cases were discovered in the Italian and French armies, others soon reported from Eng-

land and South America, and later it became clear that the disease existed in the United States. The localities in which the condition is said to have been noted include New York, Ohio, and Missouri. According to Bloedorn and Houghton, the disease is more widespread than is generally recognized, and according to Greer, it is prevalent in the Southern States.

**SYMPTOMS.**—Castellani recognized an *acute* bronchospirochetosis marked by fever, weakness, cough, and scanty, mucous expectoration, lasting 1 to 3 weeks, and a *chronic* form, manifested by an insidious cough, often marked in the morning, muco-purulent expectoration, at times bloody, sometimes hemoptysis, with or without a hectic-like fever in which, in some cases, the temperature rise occurred in the mornings rather than the afternoons. The chest, according to his description, showed merely a few dry or coarse moist râles, and the general condition sometimes remained fairly good for a long time, the course of the disease being, as a rule, very prolonged. He also recognized transitional cases between the acute and chronic forms (subacute types).

Further clinical information has been supplied, among others, by Violle, who, observing cases in France, called especial attention to the peculiar brilliant pink, gooseberry-juice color of the sputum, which he describes also as markedly homogeneous and mucoid. He found the cough worse at night. Physical examination often revealed little, though at times there were signs of bronchitis with or without emphysema, or signs of consolidation. Frequently there was no fever. Some patients were anemic. The sputum showed enormous numbers of spirochetes.

Again, Nolf designated a number of cases he saw during the war as "fetid spirillar bronchitis and pulmonary gangrene," and believes this condition should be differentiated from Castellani's bronchospirochetosis as well as from Violle's hemorrhagic bronchitis.

According to Huizenga there may occur in the acute cases, aside from the cough and fever, chills, pain in the chest and night-sweats, with foamy and sometimes bloody sputum. In the chronic cases actual hemoptysis may take place.

**ETIOLOGY.**—Castellani described a polymorphic *Spirochata bronchialis* as the etiologic agent. He recognized 4 forms of the organism, varying as to their thickness, length, and number of coils, admitting, however, that his appellation might actually cover several varieties of spirochetes and possibly different species. Violle gives the length as from 4 to 30 microns, usually 7 to 14. Some organisms had very few coils; others, a large number very close together. Bloedorn and Houghton state that the disease appears to be transmissible from an infected to a non-infected individual, and recognize the existence of healthy carriers of *Spirochata bronchialis*.

Report of 6 cases from Cairo, Egypt. There is a tendency to group together the various parasitic spirochetes of the mouth, teeth, pharynx and bronchi and to consider them, if not a single species, at least as capable in such localities of provoking identical lesions and symptoms. The fact that all the writer's cases presented pyorrhea alveolaris is regarded by him as supporting this view. Doubt is even thrown on the separate identity of the fusiform bacilli and the spirochetes of Vincent. Films from his 2d case gave results identical with those obtained in the most typical cases of Vincent's angina, in spite of the absence of symptoms of the latter. These films also showed forms intermediate between the fusiform bacillus and spirochete of Vincent, suggesting that the bacillus is merely an encysted form of the spirochete. He concludes that the fuso-spirillar organisms of Vincent may—seemingly after pyorrhea as their first localization—establish themselves in the bronchi and provoke a bronchitis of the Castellani type. His cases were all chronic from the first and apparently not contagious. Y. Schwarz (Lancet, Dec. 27, 1924).

Case in which tubercle bacilli were present along with the Castellani spirochete. The spirochetosis is regarded as having been primary. Fernandez (Gac. méd. de Caracas, xxxii, 182, 1925).

**DIAGNOSIS.**—The acute type, according to Castellani, may be mistaken for in-

fluenza or malaria; in the latter condition, examination of the blood would prove diagnostic.

The chronic cases are usually mistaken for tuberculosis, though Violle saw some reported as bronchitis with hemoptysis, pneumonia, or pulmonary congestion. In an individual in fair health with bright pink sputum bronchospirochetosis should be suspected. Tuberculosis is excluded by a sputum persistently negative for tubercle bacilli, as well as by animal inoculation and tuberculin tests. Mixed infections of tuberculosis and spirochetosis do, however, occur.

The essential diagnostic measure is the finding of *Spirochata bronchialis* in the sputum. The organism may be stained by the Fontana method or with congo red, carbol-gentian, Leishman's or Giemsa's stains. Before collecting the sputum the mouth should be carefully washed, to exclude insofar as possible the spiral organisms normally found in this cavity. Exclusion of hyphomycetes and of the ova of *Paragonimus westermani* may be advisable. Repeated examinations for the spirochetes may be necessary in the chronic cases, but in the acute cases they are numerous.

*S. bronchialis*, 5 to 30 microns long and exhibiting 4 to 8 spiral coils, is frequently visible in fresh sputum specimens, but may with advantage be fixed by heat and stained with gentian-violet. The germ may invade the bronchi because of impaired resistance from anemia or other sources of lowered vitality, or may follow acute colds or bronchitis. L. S. Huizenga (Ned. Tijds. v. Gen., Dec. 22, 1923).

**TREATMENT.**—Arsenic and arsphenamin appear to have given the best results in the chronic form. E. C. Faust has reported excellent results in 5 cases in China-men from repeated intravenous injections of 0.6 Gm. of neoarsphenamin, the spirochetes soon disappearing from the sputum of these patients.

Of the cases seen by Schwarz all were cured by 1 or 2 intravenous injections, except 1 case of 8 years' duration, in which 8 weekly injections of 0.15, 0.2, 0.3, 0.45, 0.45, 0.6, 0.6 and 0.6 Gm. were given, and

temperature reduction and recovery began only after the 7th injection. He quotes N. Farah, however, as not having been satisfied with the results from neoarsphenamin and as employing only iodine in the form of **lipiodol** in intramuscular injections of 2 c.c. daily, then spaced, always with very good, though somewhat slow, results.

Castellani has advised **tartar emetic**,  $\frac{1}{2}$  grain (0.005 Gm.) every two hours in solution in syrup of tolu and chloroform water. **Rest, fresh air, and generous diet** proved effective in Violle's cases. Vaccarezza obtained a cure in a case of recurring hemoptysis of 4 years' standing by injecting **iodized oil**, up to 10 c.c. ( $2\frac{1}{2}$  drams) daily for 10 days, followed by oral iodine treatment. **Ergotin** and **tincture of iodine**, a few drops well diluted, may be given if hemoptysis is severe; **opium** preparations, if there is much secretion and cough is painful.

The writer discovered 76 cases of bronchospirochetosis in tuberculosis sanatoriums and elsewhere in Caracas, Venezuela. The disease seems to be transmissible, and **antimony** intravenously is the most effective treatment, though **arsenic** by mouth also proves beneficial. J. R. Risquez (Gac. méd. de Caracas, July and Aug. 15, 1923).

In China, the author gives 4 drops of **Fowler's solution** 3 times daily, reserving the more expensive neoarsphenamin, in particular, for cases complicated with recurrent fever. For the 1st week in the acute cases the patient should remain in bed. When the sputum is bloody, **calcium lactate**, 0.3 Gm. (5 grains), is given 3 times daily. **Acetylsalicylic acid** may be given for pain and the cough controlled with various cough mixtures. Huizenga (Ned. Tijds. v. Gen., Dec. 22, 1923).

Case in which arsenicals, antimony, iodides and balsams all failed, and **direct local treatment** was deemed advisable. The writers, like Schwarz, found a fusiform bacillus in conjunction with the spirochetes in the sputum. Cassaët, Bonnin and Guénard (Gaz. hebdom. des sci. méd. de Bordeaux, Apr. 13, 1924).

**BUCHU** consists of the leaves of *Barosma betulina*, of *Barosma crenulata*, or of *Barosma serratifolia*, shrubs of the natural order Rutaceæ, native of South Africa. They contain a volatile oil which is doubtless the active principle and includes a camphor-like body, **diosphenol**; a bitter extractive, **barosmin**; a resin, a gum, and lignin. The oil has a peppermint-like odor.

**PREPARATIONS AND DOSE.**—*Fluidextractum buchu* (fluidextract of buchu).—Dose, 30 to 60 minims (2 to 4 c.c.), three times daily for an adult; 10 to 30 minims (0.6 to 2 c.c.) for a child. It should be well diluted before taking.

An infusion of buchu, unofficial, is also sometimes used. It is made by adding an ounce of the leaves to a pint of water. Dose,  $\frac{1}{2}$  to 2 ounces (15 to 60 c.c.). The B. P. recognizes a 5 per cent. infusion, employed in the same dosage.

**PHYSIOLOGICAL ACTION.**—A sense of warmth is imparted to the stomach by small doses; this gradually diffuses over the body. The pulse rate is increased, appetite stimulated, and slight diaphoresis induced. The drug increases slightly the flow of urine, which tends to become dark in color, acquires a strong aromatic odor, and may deposit a brownish sediment. The urine is rendered slightly antiseptic by buchu. Large doses produce vomiting, purging, and strangury, with a burning sensation in the stomach.

**THERAPEUTIC USES.**—Buchu is used in chronic catarrhal conditions of the genitourinary tract. The oil acts as a stimulant to the mucous membranes of the kidney and the genitourinary passages, and also exerts an alterative effect on them if diseased. It is thus a useful remedy in **chronic pyelitis**, **subacute** and **chronic cystitis**, **vesical irritation** (especially of the neck of the bladder), **prostatitis**, and **urethritis**. The drug has also been administered in **chronic bronchitis**, **chronic rheumatism**, **atonic dyspepsia**, **lithiasis**, affections of the skin, and **dropsy**. W.

**BUERGER'S DISEASE (Thromboangiitis obliterans).**—A condition which may be mistaken for Raynaud's disease has been described by Leo Buerger, of New York, under the term *thromboangiitis obliterans*. It occurs usually in male Russian



Jews of middle age, and has been shown by Buerger to be due to acute inflammatory lesion and consequent occlusive thrombosis of arteries and veins, the lesion involving deep veins in about 40 per cent., and the superficial veins of the upper and lower extremity in 20 per cent., of the cases. The disorder, or a similar condition, had already been referred to by such terms as *endarteritis obliterans*, *arteritis obliterans*, *arteriophlebitis obliterans*, *spontaneous gangrene* and *presenile gangrene*.

**SYMPTOMS.**—The condition is well developed when the patient first applies for treatment. The early symptoms are tingling, formication, a sensation of cold, and pain in the part involved, usually one foot or lower extremity, the opposite limb sometimes becoming affected later. The pain may have been felt for years, coming on at night on account of the warmth of the bed. It is usually pronounced, but is present a long time before trophic disturbances appear. Upon locomotion or fatigue, a painful, intermittent lameness sooner or later appears, the pain usually disappearing after rest. There is tenderness of the calf muscles, and the great toe often exhibits a dusky red color. Involvement of the upper extremity is characterized by limited motion of the fingers and sometimes slight edema. An important feature is that as the limb is lowered from the horizontal position to the vertical it becomes red or purplish up to the knee. In severe cases the red color may not return until the vertical position has been almost or entirely reached. The angle at which it returns is deemed of prognostic import. Absence of pulse in the *dorsalis pedis*, posterior tibial, popliteal, radial, or ulnar arteries may be observed. Trophic disturbances are variable, and consist of ulceration, ecchymosis and edema. The ultimate consequence is gangrene of the toes or of the whole foot or leg.

**ETIOLOGY.**—The multiplicity of theories suggested as to the origin of this disease indicate, according to B. Jablons, a variety of causes. In the majority of cases some pre-existing injury to the blood-vessels has occurred, either from frost-bite or trauma followed by infection and consequent arteritis and phlebitis. Buerger believes some bacterial agent responsible. The leukocytes

seem to be affected, the average count in 50 or more cases having been about 11,000; the lymphocytes exceeded their normal count by about 10 per cent. In most cases a definite eosinophilia was present. Many patients show a markedly accelerated coagulation time. According to Heitz, diabetes, syphilis and tobacco abuse are outstanding factors in *endarteritis obliterans*; an excess of blood cholesterol, averaging 2.77 Gm. per liter, was found in 27 cases. W. G. Stern states that angiotrophosis, which includes Buerger's disease, is the only disorder with normal erythrocyte count in which high blood viscosity is common.

**PATHOLOGY.**—According to MacCallum, the lumen of involved vessels in cases of this type is found to be filled with granulation tissue, sometimes with endothelium-lined spaces through which a little blood may flow. Koyano found in 1 case "a purulent focus and giant-cell foci" in an occluded superficial vein. Telford and Stopford found the arterial intima slightly thickened, the media poor in muscle tissue, and the adventitia greatly thickened, reducing the lumen.

**DIAGNOSIS.**—Although the limb is sensitive to cold, damp weather and is colder than its fellow, the characteristic local asphyxia of Raynaud's disease is not present. Of diagnostic utility is the *Parkes Weber sign*, consisting of a change from redness to marked pallor of the affected limb when it is repeatedly flexed and extended. Gilbert and Coury lay stress on the lack of effect of a cold bath at 48° F. on the limb, and the marked pink color for 4 or 5 minutes, without change in arterial pressure in the limb, following a hot bath at 110° F. They refer also to a marked lowering of the arterial, especially systolic, pressure in the limb, and an almost complete disappearance of the sphygmomanometric oscillations when gangrene threatens. Regarding the blood, they mention an increase in red cells, seldom exceeding 6 million; an increase of blood sugar without glycosuria, occurring in over half the cases; a reduction of the bleeding time, and an increase of blood viscosity. Anginal pain, general hypertension, evidences of renal deficiency, nervous disturbances, bone changes, and syphilitic manifestations are all absent. *Erythromelalgia* is excluded by the arterial

pulsations which accompany it, and other evidences. *Raynaud's disease* is symmetric, usually in females, causes less pain, and shows attacks induced by cold; the blood picture and etiology also serve in differentiation.

**TREATMENT.**—During the earlier stages relief from pain is sometimes obtainable by allowing the foot to hang down. Application of **heat** may also give temporary comfort in some cases. Prolonged **rest in bed**, to enhance local nutrition and delay the progress of the disease, is strongly advised. Gilbert and Coury suggest **alternate hot and cold bathing** of the affected limb. **Analgesic drugs** may be required. Tobacco should be interdicted. For trophic conditions they recommend **hot air treatment**; for ulcers, **balsam of Peru** may be used. Among surgical procedures, **amputation** is the only effectual proceeding. It should, however, be done only as a last resort, as remission in the disease may take place, and when done, should be conservative. It should be preceded by thorough trial of the treatment described by W. A. Steel, which follows:—

During the first month the patient is kept in **bed** with the legs constantly in either a **hot air** or **electric light bath** at 110° F., and 250 c.c. (½ pint) of 2 per cent. **sodium citrate** solution is given intravenously every second day. During the second month the interval of injection is lengthened to every third or fourth day, daily **leg massage** is given and the patient put in a wheeled chair with feet hanging down for a short time each day; or, if the case is not advanced, some walking is allowed. The intervals of injection are then gradually lengthened until 1 is given every 2 weeks. **Potassium iodide** in 10-grain (0.6 Gm.) doses 3 times daily is given during the whole course of treatment.

Thromboangiitis obliterans observed in 4 men between the ages of 30 and 40. None showed syphilis or arteriosclerosis, and the diet of all was chiefly vegetarian. The disease occurred during the colder months of the year. Treatment was **rest in bed**, **elevation** of the foot, **bathing with hot hypertonic saline solution** or **alternating hot and cold baths**, and **amputation** of gangrenous tissue. The writer recalls Meyer's suggestion of a disturbance of

carbohydrate metabolism with tendency to hyperglycemia, which calls for treatment by **abundance of water** through simultaneous use of **duodenal flushings** and **hypodermoclysis**. A. I. Ludlow (*China Med. Jour.*, Jan., 1920).

Two cases in which, after other methods had failed, distinct improvement was obtained from **duodenal irrigation with Locke's solution** for 10 days, as recommended by McArthur. Pain was suppressed in some cases and amputation rendered unnecessary or postponed in others. Pasman (*Rev. Assoc. méd. Argén.*, xxxiii, 146, 1920).

Blocking of pain transmission by **injection of absolute alcohol** into the posterior tibial nerve at the level of the internal malleolus gave good results in 3 cases. The nerve was exposed, anesthetized with **procaine**, and then injected thoroughly for some distance with the alcohol. Anesthesia of the sole, with relief of pain, resulted, persisting for 6 months. The wounds healed firmly, and no trophic disturbances followed. Silbert (*Jour. Amer. Med. Assoc.*, Nov. 18, 1922).

Three out of 4 cases greatly benefited by the use of **sodium citrate** and **iodides**. **Benzyl benzoate** seemed of value in relaxing the affected vessels. **Stovaine** or **zinc oxide ointment** was used for the relief of local pain. Simonema (*Siglo méd.*, Apr. 26, 1924).

Case in a man of 45 years who was not a Hebrew. Involvement of 1 of the brain arteries, producing partial hemianopsia, was superadded. The increase of blood cholesterol suggested increased adrenal activity and a resulting disturbance of lipoid metabolism. Gradual moist gangrene of ⅔ of the foot was successfully met by giving **sodium citrate** intravenously (28 injections) and the use of **hot air** and dressings of **ether**. Arrest of the gangrene, with subsequent sloughing, and cessation of pain soon resulted, and after 9 months the patient was entirely well. A course of **neo-arsphenamin** injections had also been given on account of an earlier slightly positive Wassermann reaction. In the use of sodium citrate in such cases,

the writers advise at the start daily injections of 6 or 4 Gm. ( $1\frac{1}{2}$  or 1 dram) of sodium citrate in a 30 per cent. solution. Later, the intervals between injections may be lengthened to 2 or 3 days, or the citrate given by hypodermic injection or by the mouth. J. Troisier and A. Ravina (Bull. Soc. méd. des hôp. de Paris, May 15, 1924).

The treatment for acute cases consists of **rest in bed**, a **bland diet**, continuous **electric light baths** to the extremities, introduction of 4000 to 6000 c.c. of **Ringer's solution** through the **duodenal tube**, and **sodium iodide intravenously**. Upon subsidence of the acute symptoms, there should be a complete **change in the habits** of the patient in order to reduce functional demands on the local circulation, with **avoidance of all forms of toxic absorption**, ingestion of large quantities of **water**, and the circulation **exercises** devised by Buerger. At all times the body should be protected from being chilled or compressed. Stern (Jour. of Bone and Joint Surg., Oct., 1924).

Five cases occurring in white Gentiles, all of whom had oral infection. The treatments tried comprised hot and cold applications, injections of salines and sodium citrate intravenously, Locke's solution, Ringer's solution, typhoid vaccine, vessel exercise, ligation of femoral vein, arteriovenous anastomosis, periarterial sympathectomy and amputation. **Amputation** was the only measure giving any considerable relief. Thurston (U. S. Vet. Bur. Med. Bull., Dec., 1925). S.

**BULBAR PARALYSIS.**—Two types of this disease have been recognized: **ACUTE BULBAR PARALYSIS**, or **ACUTE INFERIOR POLIOENCEPHALITIS**, and **CHRONIC (PROGRESSIVE) BULBAR PARALYSIS**, or **LABIOGLOSSOLARYNGEAL PARALYSIS**.

#### **ACUTE BULBAR PARALYSIS.**

**SYMPTOMS.**—The onset is characterized by the usual signs of an infectious invasion, *viz.*, headache,

vertigo, chills, and fever. Rapidly a paralysis of the muscles supplied by various bulbar nerves makes its appearance. The tongue, lips, palate, and larynx are first affected. Sometimes the muscles of the face and the external recti muscles of the eyeballs are involved. The inability of retaining food in the mouth, the difficulty of swallowing, the projection of liquids and food through the nose during the attempts at swallowing, the nasal intonation of the voice, the difficulty of breathing—are all the characteristic clinical manifestations of the disease. Its course is usually rapid; it lasts but a few days. In exceptional cases, however, it may be prolonged to a few weeks. The outlook is always grave. Death is usually the result of suffocation. Occasionally recovery has been observed (Eisenlohr). The writer observed an almost complete recovery in a case of acute bulbar palsy occurring in the course of diphtheria in a girl of 14 years.

**DIAGNOSIS.**—The above symptoms and their sudden or rapid onset are so characteristic that the disease can be easily recognized. Some difficulty, however, may be experienced in differentiating it from sudden "pseudobulbar palsy." But in the latter affection the symptoms of muscular paralysis are much milder than in the first; besides, in most cases there are usually two distinct attacks, and only the last produces a distinct paralysis of the lips, tongue, and pharynx. Finally, in pseudobulbar palsy there are always indications of a lesion in one or the other cerebral hemisphere, such as hemiplegia.

#### **ETIOLOGY AND PATHOLOGY.**

—Acute bulbar palsy has been observed in the course of infectious diseases,

such as diphtheria, scarlet fever, pneumonia, and typhoid fever. Grave alimentary intoxications may also be followed by acute bulbar symptoms. The disease may occur in chronic alcoholism and in syphilis.

The lesion consists of foci of hemorrhages or softening. The gray matter, the white matter, and the nuclei of the bulbar nerves may be simultaneously affected. The maximum of involvement is at the level of the nuclei. All the nerves, except the third, fourth, and the sixth, may be affected. Sometimes a combined, viz.: an inferior and a superior, polioencephalitis is observed. In such cases the nerves of the upper and lower portions of the medulla are simultaneously involved. Microscopically the medulla appears in a state of inflammation, to wit: the blood-vessels are dilated, congested; the perivascular spaces are filled with leucocytes; the cells of the nuclei are in a state of chromatolysis, and the axis-cylinders undergo degeneration. In Eisenlohr's case taken from a typhoid-fever patient who died with symptoms of acute bulbar palsy, microbes were found in the medulla. Gerson has observed and reported 2 cases of myasthenic bulbar paralysis due to diphtheria. The symptoms appeared at intervals, beginning with progressive weakness of the muscles of the lips and tongue and of the facial muscles.

**TREATMENT.**—Counterirritation applied to the neck and purgatives are the immediate means. Special attention must be paid to the feeding. In view of the difficulty of swallowing, the patient is in constant danger of suffocation. When a history of syphilis is obtained, injection of salvarsan may be tried.

### **CHRONIC (PROGRESSIVE) BULBAR PARALYSIS, OR LABIOGLOSSOLARYNGEAL PARALYSIS.**

**SYMPTOMS.**—The onset is slow, but progressive. It is usually preceded by some vague pain in the neck. Gradually a weakness of the tongue is noticeable. The patient experiences some difficulty in moving it in the mouth during the act of mastication or in speaking; also in protruding it. At the same time or shortly afterward the lips become affected. The palate follows next in order. Finally, the muscles of the pharynx and the larynx become involved.

When the disease is at its beginning, the striking disturbance is in the tongue. The letters which require the use of the tongue are poorly pronounced; the speech is indistinct (dysarthria). In a more advanced period of the disease not only marked limitation of movements of the tongue is observed, but the organ appears flat and flabby, it is atrophied, and fine fibrillary contractions are noticeable. At this stage the speech is almost impossible (anarthria). Reactions of degeneration are present. Mastication is very difficult, and the food remains a long time in the mouth. The muscles of the lips undergo atrophy, and the patient is unable to execute the act of blowing and whistling. During the act of speaking they remain immobile. The mouth is open, and the saliva is continuously dribbling. The facies is then characteristic. It gives the impression of mental hebetude, and this is particularly noticeable in the act of laughing. The patient does it with a widely open mouth and for a sufficiently long time to impress as being stupid. A tendency to keep on laughing when once started is somewhat

characteristic of the disease. The silly facies is only apparent, as in reality there is complete preservation of mental faculties.

The condition of the muscles of the lips increases the difficulty of speaking and especially in pronouncing labial letters. Fibrillary contractions and reactions of degeneration of the muscles of the lips are present.

The paralysis of the palate is manifested by the nasal intonation of the voice; in order to improve the pronunciation the patient closes up his nostrils, so that the air during the act of speaking passes entirely through the mouth. When the pharynx becomes involved, the patient's deglutition is embarrassed. The food is rejected through the nose and the mouth. The patient uses all sorts of subterfuge to force the food into the pharynx: he throws his head backward; sometimes pushes the food with his fingers. He is in constant danger of having particles of food penetrate into the larynx.

The involvement of the larynx is a late manifestation. In such a case speech is absolutely impossible and aphonia is complete. Besides, the danger of suffocation from food is greater. Bronchopneumonia from aspiration of particles of food into the larynx is not rare.

The involvement of the nuclei of the most important nerves naturally leads to cardiac and pulmonary complications. The latter have been already mentioned. It may, however, be added that the inability of the patient to breathe or expectorate properly leads to accumulation of mucus in the bronchial tubes, so that an ordinary bronchitis may be very serious. As to the cardiac disturbances, they consist of attacks of cardiac oppression, of attacks of syn-

cope; the pulse is small, feeble, and irregular.

*Infantile pseudobulbar paralysis* observed in 17 dispensary patients, including 2 between 24 and 26 years of age. One of the latter had so much speech difficulty that he had to communicate in writing. In none of the patients was mentality affected, though an appearance of imbecility was produced by the open mouth and dribbling. Dysarthria was the chief manifestation, with a nasal tone due to paralysis of the soft palate. No muscular atrophy is present, as the disorder is in the cortex, not in the medulla. Such cases are probably more common than has been thought. These children should not be classed with the backward, as they advance more rapidly with children of their own mental grade. They are usually able to learn to overcome the difficulty and the prognosis is generally favorable. The paralysis of the soft palate should be combatted by means of speech exercises. M. Fiebig (Arch. f. Kinderheilk., Feb. 1, 1921).

Among other symptoms of labioglossolaryngeal paralysis may be mentioned the increase of the patellar tendon-reflexes, which has been observed in the majority of cases, although not in all. This fact speaks in favor of the view that progressive bulbar paralysis is a form of amyotrophic lateral sclerosis (see Pathology).

Progressive bulbar palsy may sometimes develop in the course of progressive muscular atrophy. It is then an indication that the pathological process of the latter disease, which consists of a progressive destruction of the cells of the anterior cornua of the cord, has reached the medulla and involved the cells of the nuclei.

When, in the course of such cases, the progressive muscular atrophy is at its climax, a gradual involvement of the lips and tongue begins to be noticeable.

**DIAGNOSIS.**—There is no difficulty in recognizing the affection from its slow onset, gradual and progressive involvement of the muscles of the tongue, lips, pharynx, and larynx. However, a difficulty of swallowing, of opening the mouth, of moving the tongue may be encountered in acute tonsillitis or pharyngitis. In the latter affections there will always be fever, pain, adenopathy, which are wanting in bulbar palsy.

Bilateral facial paralysis may simulate progressive bulbar palsy through the immobility of the facies, but it should be borne in mind that in the latter affection the upper part of the face is not involved and in the first affection the muscles of the tongue, larynx, and pharynx are not involved.

Difficulty of deglutition, nasal intonation of the voice may be caused by paralysis of the palate in the course of or following diphtheria, but there is no involvement of the tongue or lips.

Pseudobulbar palsy always follows one or two apoplectic seizures. The symptoms of bulbar paralysis are only slightly marked after the first attack, but are distinct after the second attack. However, there is no slow, progressive, and successive involvement of the tongue, lips, and pharynx. Besides, there is always present a hemiplegia. The muscles affected do not show reactions of degeneration or fibrillary tremor. Intelligence is diminished, and there is a spasmodic laughing or crying.

In myasthenia gravis there is a weakness of the muscles of the tongue, larynx, palate, and pharynx, but there is a predominance of weakness in the masticatory muscles and in the levator palpebræ. Ptosis is evident. Besides, the general asthenia, the absence of atrophy, of reactions of degeneration,

of fibrillary tremor, the presence of the special myasthenic electrical reaction consisting of rapid exhaustion of muscular contractions—are all sufficient to distinguish this affection from progressive bulbar paralysis.

**ETIOLOGY.**—The true causes of the disease are not known. It has been observed in the course of amyotrophic lateral sclerosis, progressive muscular atrophy, syringomyelia, tabes, multiple sclerosis. Debilitating diseases, syphilis, intoxications, exposure to cold, overuse of the muscles have been mentioned by various authors as causes of the affection. It usually occurs in middle age, although it has been observed in children. Males are more frequently affected than females.

**PATHOLOGY.**—The morbid changes consist chiefly of a primary, but progressive degeneration of the nuclei of the nerves originating in the lower half of the medulla—viz.: in the nuclei of the seventh, ninth, tenth, eleventh, and twelfth nerves. The most marked changes are seen in the nucleus of the twelfth nerve. These changes are similar to those observed in the cornua of the spinal cord in progressive muscular atrophy. They show various stages of chromatolysis with subsequent disappearance of the cells. The axis-cylinders emanating from these cells and the roots of the nerves undergo degeneration. The interstitial tissue is also changed; sometimes there is an increase of connective tissue and thickening of the walls of the blood-vessels.

The pathological process may not be confined exclusively to the nuclei. Not infrequently the white matter of the medulla has been found affected. Degenerative changes in such cases have been traced in the pyramidal bundles through the pons and cerebral pedun-

cles. Otherwise speaking, progressive bulbar paralysis may be an amyotrophic lateral sclerosis. According to Leyden, this is always the case; Raymond, Dejerine, and others have admitted that, while an involvement of the white matter is a frequent occurrence, nevertheless, an independent nuclear involvement, such as Duchenne originally described, is also possible.

The muscles in which the degenerated bulbar nerves are distributed undergo atrophy. Their size is diminished; the nuclei of the sarcolemma proliferate; the interstitial and fatty elements are increased.

The muscles involved in the atrophy are those of the tongue, lips, pharynx, and larynx.

**PROGNOSIS.**—The disease is essentially progressive. Remissions, or temporary arrests of development, are sometimes observed. It may last from a few months to several years. There are no cases of cure on record. Death may result either from inanition because of the difficulty or inability of swallowing, from bronchopneumonia caused by penetration of food into the air passages, or from sudden involvement of the heart in attacks of syncope. The prognosis in this condition is invariably grave.

**TREATMENT.**—There is no special medication that could arrest the course of the disease. Local **cauterization** of the neck, antisyphilitic remedies: **mercury**, the **iodides** and **salvarsan**, and also **strychnine**, **nitrate of silver**, **arsenic**, **phosphorus**, **electricity** applied to the neck or to the affected muscles—may all be tried, but not much reliance can be placed on any of the remedies.

When the patient has difficulty in swallowing, he must be fed through

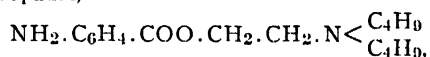
an esophageal tube. In case of suffocation, **tracheotomy** must be performed.

ALFRED GORDON,  
Philadelphia.

**BUNION.** See TENDONS: BURSTITIS.

**BURNS.** See SKIN, SURGICAL DISEASES OF.

**BUTYN.**—This local anesthetic is chemically para-amino-benzoyl-dibutylamino-propanol,



and is somewhat similar in composition to procaine.

Butyn has been credited, from the standpoint of ophthalmologic use, with the following properties: More powerful than cocaine; more rapid and prolonged action; less toxic; no drying effect; no change in the size of the pupil; no ischemic effect and consequently no shrinkage of tissue; no impairment of anesthetic efficiency on boiling.

According to animal experiments and clinical tests by Schmitz and Loevenhart, butyn probably has no advantage over cocaine for anesthesia of the intact mucosa. It is more efficient than cocaine for anesthetizing the cornea, but this advantage is offset by its greater toxicity. For paralysis of sensory nerve trunks it is only  $\frac{1}{2}$  as efficient as procaine and about 10 times as toxic.

Comparing butyn with cocaine in laryngeal work, Sir St. Clair Thomson found the former to be slower in action and much less effective; it may produce an irritating amount of secretion, and can evidently be extremely toxic. Of whatever value it may be in the eye, ear, nose, or pharynx, it seemed wholly disadvantageous in laryngeal work.

Dermatitis in a genitourinary specialist was traced to the use of butyn by Greenwood and Quest (Jour. Amer. Med. Assoc., Oct. 4, 1924). Beginning with a vesicular eruption on the hands and arms, the condition recurred with swelling and itching of the genitalia, and later a universal papular, itching eruption, becoming pustular. S.

**CACODYLIC ACID** and its salts, the **CACODYLATES**, constitute a series of organic arsenic compounds containing the basic radical cacodyl  $(\text{CH}_3)_2\text{As}$ . Sodium cacodylate is official as *Sodii cacodylas*.

The formula of cacodylic acid, or dimethylarsenic acid, is  $(\text{CH}_3)_2\text{AsO} \cdot \text{OH}$ . It occurs in the form of colorless, odorless crystals, with a slightly sour taste, and is soluble in water and alcohol. It contains 54.3 per cent. of elemental arsenic.

*Sodium cacodylate*  $[(\text{CH}_3)_2\text{AsO} \cdot \text{ONa} + 3\text{H}_2\text{O}]$  appears as an amorphous, white powder, or crystals, easily soluble in water. The fluid resulting from its dissolution is alkaline in reaction toward litmus, but is practically neutral toward phenolphthalein. Sodium cacodylate, while chemically a stable substance when in the dry state, absorbs water from the air. When kept in solution, it tends to deteriorate after a time (Arnozan). It contains 36 per cent. of pure arsenic.

*Sodium methylarsenate*, or *arrhenal*  $[\text{CH}_3 \cdot \text{AsO} \cdot (\text{ONa})_2 + 5\text{H}_2\text{O}]$ , greatly resembles sodium cacodylate in action. It occurs as white crystals, readily soluble in water and slightly so in alcohol. It contains 33 per cent. of arsenic.

**DOSE AND MODES OF ADMINISTRATION.**—The dosage of cacodylic acid, sodium cacodylate, and sodium methylarsenate in adults ranges from  $\frac{1}{4}$  to 3 grains (0.016 to 0.2 Gm.) per diem. In children 6 to 10 years old the maximal daily dose is  $\frac{1}{3}$  to  $\frac{1}{2}$  grain (0.02 to 0.03 Gm.), and in those 3 or 4 years old  $\frac{1}{6}$  grain (0.01 Gm.) (Rocaz).

These drugs, though often used in-

ternally, are, in addition, especially suitable for hypodermic injection, causing no local irritation except in large doses. According to Gautier, as much as  $1\frac{1}{2}$  to 3 grains (0.1 to 0.2 Gm.) per diem will be retained by the stomach for an indefinite period. Administration of the drug by enema has also been carried out,  $\frac{1}{10}$  to  $\frac{1}{6}$  grain (0.006 to 0.01 Gm.) in water two or three times daily.

Renaut suggests the following solution for use by rectum:—

$\mathcal{R}$  *Sodium cacodylate* . 4 to 6 gr. (0.25 to 0.40 Gm.).  
*Water* .....  $6\frac{1}{2}$  oz. (200 c.c.).  
 M. Sig.: Use 80 minims three times a day.

Mendel found intravenous injections of a 5 per cent. solution safe and reliable in 400 cases.

**PHYSIOLOGICAL ACTION.**—The effects of cacodylates are essentially those of arsenic, exerted more slowly owing to the fact that the arsenic does not develop its accustomed action until it has been liberated from the firm organic combination in which it is present in the cacodylic compounds. Since this liberation takes place only in relatively small amount, Heffter's experiments having indicated that but 2 or 3 per cent. of sodium cacodylate is decomposed with liberation of the arsenous ion, the action of the drug is correspondingly weakened.

Dawes and Jackson detected the drug in the urine after daily hypodermic injections in from 10 to 36 days or more. Inorganic arsenic began to be eliminated in 2 cases after 22 and 44 days, respectively. Only a small portion of the injected drug is eliminated through the urine.



Cacodylates exert effects on the blood and on general nutrition similar to those of inorganic arsenic. De Biehler found a distinct increase of body weight to occur in rabbits given sodium cacodylate over and above that taking place in the same period of time in control animals. The results obtained with cacodylates in cutaneous affections also suggest that their action on the skin is the same as that of arsenic in inorganic form.

According to Dawes and Jackson, cacodylic acid is deposited in the body tissues, and then gradually in part decomposed. The amount of arsenic eliminated in the urine was found to vary in different persons.

A pronounced garlic-like odor of the breath is frequently observed in those taking cacodylates, whether by mouth or hypodermic injection. This is believed due to the formation of the strongly smelling compound cacodylic oxide, by partial decomposition of the drug. One of Dawes's patients treated with sodium cacodylate reported the odor of garlic in the perspiration about a week after injections of 3 grains (0.2 Gm.) had been commenced. Complaint of the odor in the urine is not an infrequent occurrence; this odor may also be observed in inorganic arsenic medication.

**UNTOWARD EFFECTS AND POISONING.**—While cacodylic compounds were at first claimed to be "non-toxic" and devoid of the unpleasant collateral effects of inorganic arsenic compounds,—diarrhea, pigmentation of the skin, paralyses,—clinical experience with them has shown that this is only relatively true. Wm. Murrell has reported a case which shows that sodium cacodylate may produce all the untoward systemic

effects of arsenic in a marked and decided manner.

**THERAPEUTIC USES.**—Sodium cacodylate is of value in the same classes of affections as inorganic arsenic preparations, and appears to be most suitable for cases where a prolonged arsenical action is required.

In **anemias**, especially of the **pernicious** type, it has given good results in the hands of a number of observers. In **simple anemias**, it has shown evidence of its power greatly and, as a rule, rapidly to increase the hemoglobin percentage as well as in many instances the number of red cells. Administration by hypodermic or intramuscular injection is the procedure of choice; Dawes found that the drug does not cause discomfort at the site of injection unless given in very large doses, such as  $4\frac{1}{2}$  to 9 grains (0.3 to 0.6 Gm.). The method employed by this author is to have the pharmacist weigh out various doses— $1\frac{1}{2}$ ,  $2\frac{1}{4}$ , 3, and  $4\frac{1}{2}$  grains (0.1, 0.15, 0.2, and 0.3 Gm.)—and place them in sterile  $\frac{1}{2}$ -dram (2 Gm.) phials. At the time of injection the dry salt is placed in the barrel of the syringe, which has been previously sterilized. Boiling water is then drawn into the syringe until all the salt is dissolved. When the solution is cooled to about body temperature, the needle is quickly plunged deeply into the gluteal muscles and the solution slowly injected. The initial dose is  $\frac{1}{64}$  grain (0.001 Gm.) for each pound of body weight; later the total dose is gradually increased to 3 grains (0.2 Gm.) and frequently to  $4\frac{1}{2}$  grains (0.3 Gm.). Relatively large doses daily without intermission, and often for several weeks, are best. Of 14 cases of **pernicious anemia**, 5 seemed cured, from 15 to 37

months having elapsed since treatment without recurrence.

In pulmonary and other forms of **tuberculosis**, as well as in cachexias from various causes, including **malaria**, sodium cacodylate may be given with advantage to enhance general nutrition and in particular to improve the condition of the blood. Dawes found that cases of malaria such as are seen in former residents of tropical and semitropical regions, and which had proven refractory to the persistent use of quinine, responded very promptly and permanently to the cacodylate. Malarial **gastralgia** has been found to be favorably influenced. According to Ewart, the cacodylate has a decided influence upon the hectic fever in phthisis.

Other conditions sometimes benefited by arsenic medication in which sodium cacodylate has been tried and proven of service include **neuralgias**, **tic douloureux**, **dysmenorrhea**, **bronchial asthma**, **Graves's disease**, **diabetes**, **leukemias**, **chronic rheumatic conditions**, and **chorea**. Dawes states that of 22 cases of **neuritis** treated with the drug 16 recovered. According to the same author, sodium cacodylate has proven much more satisfactory in the treatment of **chronic rheumatism** than other forms of arsenic. One case of **rheumatoid arthritis** was apparently checked by its use.

The drug has also been used by Gautier in **obesity**, **paralysis agitans**, **neurasthenia**, **myxedema**, **scleroderma**, and **sarcoma**.

Various chronic skin diseases, such as **psoriasis**, **eczema**, **lichen ruber**, and **acne**, have proven amenable to cacodylate therapy. Saalfeld, in such

cases, has given 0.1 Gm. ( $1\frac{1}{2}$  grains) of sodium or iron cacodylate daily by the mouth.

Rocaz, of Bordeaux, has recommended the use of sodium cacodylate in pediatric practice. He employed it in over 80 cases, in 60 of which the treatment was continued to its conclusion, and found that if given internally twice a day, in aqueous solution, with the meals, it is well borne by children and gives good results, notably in **anemia** and **incipient tuberculosis**. The condition of the kidneys should be examined into before beginning the treatment, and the susceptibility of the organism to the drug thereafter carefully watched. With these precautions, and by suspending the drug occasionally to guard against any tendency to cumulative action, Rocaz found it possible to avoid all disagreeable by-effects, observing neither any alliaceous odor of the breath, diarrhea, vomiting, nor skin eruptions.

The use of sodium cacodylate in **syphilis** has been suggested and more or less extensively tried. While the drug has in numerous instances proven very effective in causing the initial lesion rapidly to heal and the secondary eruption and mucous patches to disappear, experiences with it have not justified regarding the drug as in any sense a substitute for arsphenamin. The doses employed by various observers in syphilis have ranged from  $\frac{3}{4}$  to 6 grains (0.05 to 0.4 Gm.) daily subcutaneously or intramuscularly, or 3 to 6 grains (0.2 to 0.4 Gm.) by the mouth.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

**CACTUS GRANDIFLORUS.**—

This drug is obtained from the fresh (green) stems and flowers of the *Cactus grandiflorus*, Linné (*Cereus grandiflorus*, Miller and De Candolle; night-blooming cereus), a fleshy shrub bearing flowers 8 to 12 inches in diameter, growing in tropical America, especially Mexico. The drug is not official. The preparations generally used include the fluidextract, dose 2 to 10 or even 30 minims (0.12, 0.6, to 2 c.c.), and the tincture, dose 5 to 20 minims (0.3 to 2 c.c.), four times daily. An extract of the drug has also been used, in pill form. The taste of the fluid preparations is not unpleasant; von Zelenski suggests that they be given in a little water or wine.

**PHYSIOLOGICAL ACTION.**—Cactus has been claimed by some to be a heart tonic, or at least a modifier of cardiac action. It is said to increase the heart rate, strengthen the cardiac contractions, and augment the volume of the pulse; while some of the older experimenters with the drug reported results substantiating these views, more recent experimental work has thrown very serious doubt upon the circulatory effects of cactus, at least in the normal individual. Hatcher and Bailey, in experiments upon cats, dogs, and frogs with samples of cactus obtained from Mexico, found the drug practically devoid of any tangible effect upon the circulation, whether administered by mouth or vein. When given intravenously, colossal doses of cactus exerted some slight action upon the heart, but the effect was so feeble that "its nature could not be determined." The drug is thus practically inert when put to the test of modern pharmacodynamic procedures, though the possibility of the production of some slight changes of heart action in abnormal states is not necessarily precluded.

The drug is almost invariably well borne by the stomach and, so far as is known, has no cumulative effect.

**THERAPEUTIC USES.**—Cactus is said to be indicated especially in functional cardiac disorders such as nervous palpitation, in irritable tobacco or coffee heart, the irregular heart-action which sometimes follows an attack of influenza, and the irregularity and precordial discomfort consequent

upon gastric disturbance. It is claimed to act as a mild cardiac sedative and restore regularity of the heart rhythm where this is disturbed. Curtin believed it useful where cardiac irregularity "is associated with heart-strain or any other condition including dyspnea, hysteria and hypochondriasis," as well as in all emotional irregularities, sometimes in Graves's disease, when the heart is weak, irregular, and rapid; in the aged who suffer from dyspnea, asthma, and a sensation of weakness in the organ (adding to the effectiveness of nitroglycerin in these cases), and in the weakened heart of the convalescent stage of exhausting diseases.

In organic heart disease, cactus is not claimed to compare in intensity of effect with digitalis and its congeners, though several authors, including Myers and Wilcox, have reported good results from its use in aortic insufficiency. In angina pectoris cactus has also been used with asserted benefit. According to Curtin, it is useful mainly as an adjunct to heart tonics such as digitalis and strophanthus. According to von Zelenski, cactus acts well in cardiac cases contraindicating digitalis, *e.g.*, in the presence of degeneration of the heart-muscle and in bradycardia caused by vagal irritation.

On the whole, it must be said that the experimental evidence now available is not suggestive of much power on the part of cactus as a heart tonic, and that the clinical evidence is not sufficiently convincing to warrant much confidence in its action. S.

**CADE, OIL OF** (*oleum cadinum*), is a tarry oil derived from the wood of *Juniperus oxycedrus* by dry distillation. It is a thick, clear, brown liquid, with an odor of tar and a burning taste. It is but very slightly soluble in water, partially soluble in alcohol, and dissolves completely in ether, oils, and glycerin. Its constitution includes guaiacol and dioxymethylbenzol combinations.

Oil of tar (*oleum picis rectificatum*) is frequently used as a substitute for oil of cade, as it has the same therapeutic qualities, is more easily obtained, and is used in the same class of cases. It is a thin, dark reddish-brown liquid, with a strong empyreumatic odor and taste.

**MODE OF EMPLOYMENT.**—Oil of cade is generally used in an ointment, or in admixture with an equal part of olive oil, in skin diseases of the dry, scaly variety, such as psoriasis. G. Gaucher has recommended the employment of the oil in association with acetone collodion as an excipient.

The remedy can thus be applied exclusively to affected points and kept in position; it does not stain linen, and the odor of the acetone to some extent disguises that of the oil.

Oil of cade is contraindicated in inflammatory skin conditions, or when weeping or exudation are present.

**THERAPEUTIC USES.**—While not adapted for use in acute eczemas because of its irritating qualities, oil of cade is a good remedy in **chronic eczema**, especially if itching is present.

In **psoriasis** the use of an ointment of oil of cade and salicylic acid after a bath will soften the scales and tend to improve the condition of the skin.

The following ointment is useful in any dry, scaly, itching skin condition without acute inflammation:—

℞ *Olei cadini* ..... 3j (4 c.c.).  
*Acidi salicylici* ..... gr. x (0.6 Gm.).  
*Pastæ zinci*, Lassar.. 3j (30 Gm.).

M. et ft. unguentum.

Sig.: Rub well into the dry, scaly areas after a bath.

In **lichen planus** the following ointment will be found valuable, especially if itching is present:—

℞ *Phenolis* .. gr. x to xx (0.6 to 1.3 Gm.).  
*Olei cadini*. m xxx to 3j (2 to 4 Gm.).  
*Pulveris amyli*,  
*Pulveris zinci*  
*oxidi* .āā 3ij (8 Gm.).  
*Petrolati* .. 3iv (16 Gm.).

M. et ft. unguentum.

Sig.: Apply locally as directed.

According to Carle, oil of cade is efficacious only in the simple, chronic form of lichen. It may be combined with simple plaster and wax, or with starch glycerite and tincture of quillaja, or with hydrated wool-fat, cocoa butter, lard or petrolatum. One of these combinations is forcibly rubbed into the lesions in the evening and kept in place overnight by a bandage; it is washed off the next morn-

ing with soap. Itching disappears at once under this treatment.

Oil of cade mixed with an equal amount of olive oil and rubbed into the scalp several times daily is an effective remedy in **tinea tonsurans**. W.

**CAFFEINE.** See COFFEE.

**CAISSON DISEASE.** See COMPRESSED AIR; DISORDERS DUE TO.

**CAJUPUT OIL** (*oleum cajuputi*) is a volatile oil distilled from the leaves and twigs of *Melaleuca leucadendron*, a tree of the family Myrtaceæ, native of the Molucca Islands. The oil is thin, greenish, or colorless, has a camphor-like odor and a slightly bitter taste, and is neutral in reaction. It is freely soluble in alcohol and has a specific gravity of 0.915 to 0.925. It is officially required to contain 55 per cent. of the chemically definite volatile oil *cineol* (eucalyptol).

**MODE OF EMPLOYMENT.**—Cajuput oil is used internally in doses of 2 to 10 minims (0.12 to 0.6 c.c.). Externally it is used in the form of a 10 or 20 per cent. liniment.

**THERAPEUTIC USES.**—In action oil of cajuput resembles the oils of turpentine and of eucalyptus, being a stimulant to mucous membranes in small doses, but an irritant in large ones. Internally, it is effective as a carminative and anthelmintic, and is also somewhat diaphoretic. It is useful in **ascariasis**, but is chiefly employed as a gastric intestinal stimulant in **flatulent colic**, and to prevent the griping of cathartics. In **serous diarrhea** it may be tried in 10- to 20- minim (0.6 to 1.3 c.c.) doses. The drug has also been used in **hysteria**, **dropsy**, **chronic rheumatism**, **bronchitis**, **scrofula**, and **sypilis**.

Externally, as a strong rubefacient, oil of cajuput is useful in **nervous headaches**, **chronic rheumatism**, and **chilblains**; as a stimulant to the cutaneous surface, in **psoriasis**, **pityriasis**, and **acne**; and as a parasiticide, in **tinea tonsurans** and **pediculosis**. W.

**CALABAR BEAN.** See PHY-SOSTIGMA.

**CALCIUM.**—Calcium is a metal belonging to the group of the alkaline earths, and having as its atomic weight 40.1. It is not found uncombined in nature, but occurs abundantly in carbonates, sulphates, and silicates, such as marble, limestone, chalk, gypsum, selenite, and other minerals, as well as in the tissues of plants and animals. The pure metal is a silvery white, hard, malleable, and ductile substance, which slowly decomposes water, but when heated unites readily with oxygen, with the production of a brilliant white light.

Calcium is used in medicine only in the form of salts, the physiological effects of which depend, in part at least, upon their acid constituent.

#### PREPARATIONS AND DOSES.

—The official preparations containing calcium are as follows:—

*Calx* (calcium oxide; lime; quicklime) [ $\text{CaO}$ ]. Prepared from white marble or other native varieties of calcium carbonate, and occurs in hard, white or grayish-white masses. Calcium oxide is strongly hygroscopic; when left exposed to the air it absorbs both water and carbon dioxide, eventually becoming reduced to a powder. It is odorless, has a burning taste, dissolves in 840 parts of water at  $25^{\circ}\text{C}$ ., in about 1740 parts of boiling water, and is insoluble in alcohol. When to quicklime there is added about one-half its weight of water, heat is evolved, the two compounds uniting chemically with the production of calcium hydroxide (slaked lime) [ $\text{Ca}(\text{OH})_2$ ]; upon further addition of water a suspension of the hydroxide is formed which is known as milk of lime, or whitewash. Calcium oxide is used in medicine chiefly in the form of lime water and carron oil.

*Liquor calcii hydroxidi* (lime water). This fluid is a saturated solution (0.14 to 0.17 per cent.) of calcium hydroxide in water. It occurs as a clear liquid with a strongly alkaline reaction and a feebly alkaline taste. When heated, some of the contained calcium hydroxide appears as a turbidity, which, however, disappears again if the liquid is allowed to cool. Unless kept over an excess of calcium oxide, lime water gradually loses its strength through absorption of carbon dioxide from the air, which results in the formation of a precipitate of calcium carbonate. The official dose of lime water is 4 fluidrams (16 c.c.). [The *syrupus calcis* (saccharated lime solution), no longer official, is a clear, yellowish fluid, containing a much higher percentage of calcium than ordinary lime water. It was intended chiefly as an antidote for oxalic acid, a precipitate of calcium oxalate being formed, which, however, is soluble in hydrochloric acid. The dose is  $\frac{1}{2}$  to 2 drams (2 to 8 c.c.)].

*Linimentum calcis* (carron oil). Prepared by mixing equal volumes of lime water and linseed oil (*oleum lini*). Cottonseed oil might also be used. The resultant is a calcium soap of the oils employed, which is used externally as a dressing for burns.

*Calx chlorinata* (chlorinated lime; "chloride" of lime; "calcium hypochlorite;" bleaching powder), produced by the action of chlorine gas upon slaked lime, occurs as a white or grayish granular powder, having chlorine-like odor and a disagreeable saline taste. It dissolves only partially in water or alcohol, and colors litmus first blue, then white, owing to its bleaching property. Chlorinated lime gradually absorbs water and

decomposes on exposure to the air. It is officially required to yield at least 30 per cent. of chlorine gas. When added to water, it is changed to calcium hypochlorite [ $\text{Ca}(\text{ClO})_2$ ] and calcium chloride; from the resulting solution, left exposed to the air, chlorine is evolved, a process which may be greatly hastened, in conjunction with the liberation of nascent oxygen, by adding dilute hydrochloric acid to the solution or by dissolving the dry chlorinated lime in dilute acetic acid. *Calx chlorinata* is used externally and in the sick-room, cess-pools, etc., as a disinfectant. It is not employed internally.

*Calcii bromidum* (calcium bromide) [ $\text{CaBr}_2$ ]. A white, granular, odorless salt, having a sharp saline taste, very deliquescent, soluble in 0.7 part of water and in 1 part of alcohol at ordinary temperatures. Dose, 10 to 30 grains (0.65 to 2 Gm.).

*Calcii carbonas precipitatus* (precipitated calcium carbonate; precipitated chalk) [ $\text{CaCO}_3$ ]. A fine, white, amorphous, odorless, and tasteless powder, practically insoluble in water, insoluble in alcohol, and soluble in dilute acids with effervescence. The solubility of this compound is increased by carbon dioxide and ammonium salts. Dose, 5 to 40 grains (0.3 to 2.6 Gm.).

*Creta pręparata* (prepared chalk; drop chalk) consists of natural chalk—calcium carbonate—from which mineral impurities have been largely removed by suspension in water, the coarser materials present settling first and being discarded. It occurs as a white, tasteless powder, having the same solubilities as the precipitated calcium carbonate. Dose, 5 to 40 grains (0.3 to 2.6 Gm.).

*Pulvis cretę compositus* (compound chalk powder). A mixture of 3 parts of prepared chalk with 2 parts of powdered acacia and 5 of powdered sugar. Dose, 30 grains (2 Gm.).

*Mistura cretę* (chalk mixture). Made by triturating 6 Gm. of prepared chalk with 10 c.c. of glycerin, addition of 40 c.c. of cinnamon water with trituration, and rinsing with enough distilled water to make 100 c.c. Dose, 4 fluidrams (15 c.c.).

*Calcii chloridum* (calcium chloride) [ $\text{CaCl}_2$ ], made anhydrous by fusion at the lowest possible temperature, occurs in white, hard fragments, which are odorless but have a very sharp saline taste. It is soluble in 1.2 to 1.5 parts of cold water, more freely in boiling water, in 8 parts of cold alcohol and 1.5 parts of boiling alcohol. It has an exceedingly great affinity for water, and deliquesces rapidly in the air. The pure chloride gives no residue when dissolved in water, and the solution is neutral to litmus. Dose, 5 to 60 grains (0.3 to 4 Gm.); average, 15 grains (1 Gm.),—always well diluted.

*Calcii glycerophosphas* (calcium glycerophosphate) [ $\text{C}_3\text{H}_5(\text{OH})_2\text{PO}_4\text{Ca}$ ] occurs as a fine, white powder, odorless, almost tasteless, and somewhat hygroscopic. It is soluble in about 50 parts of water at 25° C., less soluble at higher temperatures; a saturated solution heated to boiling yields white, iridescent scales of it. Its solubility is increased by citric acid. It is insoluble in alcohol. A saturated aqueous solution of it is alkaline to litmus and to phenolphthalein. Dose, 3 to 15 grains (0.2 to 1 Gm.); average, 5 grains (0.3 Gm.).

*Calcii iodobehenas* (calcium iodobehenate; calioiben) consists principally of calcium monoiodobehenate [ $(\text{C}_{21}\text{H}_{42}\text{O}_2\text{I})$ ].

$\text{ICOO})_2\text{Ca}]$  and contains, when dried to constant weight at  $100^\circ \text{C.}$ , not less than 23.5 per cent. of iodine. It occurs as a white or yellowish, unctuous powder, odorless or with a slightly fat-like odor. It is insoluble in water, very slightly soluble in alcohol and ether, freely soluble in warm chloroform. When strongly heated it gives off violet vapors of iodine and white vapors with an odor of burning fat. Dose, 8 grains (0.5 Gm.).

*Calcii lactas* (calcium lactate)  $[\text{Ca}(\text{C}_3\text{H}_5\text{O}_3)_2 + 5\text{H}_2\text{O}]$  occurs in white, granular masses or powder, odorless, nearly tasteless, and somewhat efflorescent. At  $120^\circ \text{C.}$  it becomes anhydrous. It is soluble in 20 parts of water, almost insoluble in alcohol. Dose, 5 to 30 grains (0.3 to 2 Gm.); average, 15 grains (1 Gm.).

Among the unofficial preparations of calcium are the following:—

*Calcii hypophosphis* (N. F.) (calcium hypophosphite)  $[\text{Ca}(\text{PO.OH}_2)_2 \text{ or } \text{Ca}(\text{H}_2\text{PO}_2)_2]$  occurs in the form of colorless or grayish, prismatic or scaly crystals, or as a white crystalline powder. It is odorless, but has a disagreeable, bitter taste; dissolves in 6.5 parts of water, and is insoluble in alcohol. Above  $300^\circ \text{C.}$  calcium hypophosphite decomposes, giving off inflammable gases. Dose, 5 to 30 grains (0.3 to 2 Gm.); average, 8 grains (0.5 Gm.).

*Syrupus hypophosphitum* (N. F.) (syrup of hypophosphites). Contains 4.5 per cent. of calcium hypophosphite and 1.5 per cent. each of potassium and sodium hypophosphites. Dose,  $2\frac{1}{2}$  fluidrams (10 c.c.).

*Syrupus calcii lactophosphatis* (N. F.) (syrup of calcium lactophosphate). Contains a double salt of calcium in solution, and is made from 25 parts of precipitated calcium carbonate, 60

parts of lactic acid, 36 parts of phosphoric acid, and 50 parts of orange-flower water, with sufficient syrup to make 1000 parts. Dose,  $2\frac{1}{2}$  fluidrams (10 c.c.).

*Syrupus hypophosphitum compositus* (N. F.) (compound syrup of hypophosphites). Contains 3.5 per cent. of calcium hypophosphite, 1.75 per cent. each of potassium and sodium hypophosphites, 0.225 per cent. each of ferric and manganese hypophosphites, 0.11 per cent. of quinine, 0.0115 per cent. of strychnine, 0.375 per cent. of sodium citrate, and 0.5 per cent. of hypophosphorous acid. Dose, 2 fluidrams (8 c.c.).

*Emulsum olci morrhue cum hypophosphitibus* (N. F.) (emulsion of cod-liver oil with hypophosphites). Contains 50 per cent. of cod-liver oil, 1 per cent. of calcium hypophosphite and 0.5 per cent. each of potassium and sodium hypophosphites. Dose, 2 fluidrams (8 c.c.).

*Liquor hypophosphitum compositus* (N. F.). Dose, 1 fluidram (4 c.c.).

*Syrupus calcii hypophosphitis* (N. F.). Dose, 1 fluidram (4 c.c.).

*Syrupus calcii iodidi* (N. F.), containing 8.3 per cent. of calcium iodide. Dose,  $\frac{1}{2}$  fluidram (2 c.c.).

*Syrupus calcii lactophosphatis et ferri* (N. F.). Dose, 1 fluidram (4 c.c.).

*Unguentum sulphuris compositum* (N. F.) (Wilkinson's ointment; Hebra's itch ointment), consisting of precipitated calcium carbonate, 2 parts; sublimed sulphur and oil of cade, of each, 3 parts, and soft soap and lard, of each, 6 parts.

*Calcii phosphas præcipitatus* (tricalcium phosphate)  $[\text{Ca}_3(\text{PO}_4)_2]$  (N. F. V; Part II) is made from bone ash and occurs as a bulky, white, tasteless powder. Dose, 15 grains (1 Gm.).

*Calcii sulphidum crudum*, U. S. P. IX (formerly *calx sulphurata*; sulphurated lime; "calcium sulphide"; crude calcium sulphide; liver of lime) is a mixture of calcium sulphide [ $\text{CaS}$ ] (60 per cent. at least) with unchanged calcium sulphate and carbon in varying proportions. It appears as a grayish powder with an unpleasant odor and taste, which is very slightly soluble in cold water and insoluble in alcohol, but dissolves more readily in boiling water, with partial decomposition. Exposed to moist air, sulphurated lime gradually breaks down with liberation of hydrogen sulphide. The internal dose is  $\frac{1}{10}$  to 3 grains (0.006 to 0.2 Gm.); the substance is also occasionally used externally.

Calcium carbide [ $\text{CaC}_2$ ] occurs in grayish-black masses, which decompose with water, acetylene gas being evolved and a residue of slaked lime remaining. Used in gynecology as a caustic.

Dried calcium sulphate or gypsum (plaster of Paris) [ $2\text{CaSO}_4 + \text{H}_2\text{O}$ ], a fine, white, tasteless powder, is no longer official. When  $\frac{1}{2}$  its weight of water is added, a smooth paste is formed which rapidly hardens and expands.

#### PHYSIOLOGICAL ACTION.—

Lime salts form part of all animal tissues, particularly of the bones and teeth. They are also essential to the activity of certain ferments and glandular products—the thyroid secretion, for example.

Under ordinary conditions the food supplies the body with enough of the salts of calcium to satisfy the needs of the tissues (an excess being used during the process of growth) any surplus being eliminated mainly with the feces and urine.

The writer found extreme degrees of hypocalcemia in chronic undernutrition and in parathyroid tetany. Other conditions with low blood calcium were epilepsy, syphilitic aortitis or aneurism with myocardial insufficiency, general asthenia or neurasthenia, hypothyroidism, some cases of nephrosclerosis and of diabetes with acetonuria, and in the stage of exudation in lobar pneumonia. He regards hypocalcemia as 1 of the connecting links between ion action, the vegetative functions, and thyroid action. W. H. Jansen (Deut. Arch. f. klin. Med., Apr., 1924).

The ratio of the calcium to the potassium ions is of greater significance to the body than the actual concentration of these ions. Kylin (Acta med. scand., Jan. 1, 1925).

It would appear under these conditions that in such diseases as osteomalacia, rickets, etc., which are attended with deficiency of lime in the bones, the replacement of calcium salts would be indicated, but their exclusive use fails, mainly because deficient power to take up calcium underlies these disorders. Additional agencies are required to promote fixation of the calcium.

The Indians of Mexico keep their teeth to an advanced age but develop caries when they become civilized and change their dietetic habits. The early wearing out of teeth the writer explains by the fine bolting of the flour which deprives it of the phosphates, etc., in the outer part of the grain. He advises addition of earthy phosphates to the food during both pregnancy and lactation. Calcium phosphate seems indicated here. Bulman (Gaceta de la Acad. de Med., Mexico, Jan.-June, 1917).

In the dog, giving hydrochloric acid increased the urinary excretion of calcium and thereby altered the relation of calcium to magnesium in the urine. The calcium contained in milk was more effective than soluble calcium



lactate in producing calcium retention. Givens and Mendel (*Jour. Biol. Chem.*, Aug., 1917).

Communities with very hard drinking water showed less dental trouble in school-children and adults and were also better off as regards robustness and body weight of registrants for military service, the vitality of the newborn, and the frequency of nervous hyperexcitability in infants, older children, and adults. On the other hand, communities with soft water showed less calcification of the arteries. Opitz (*Deut. med. Woch.*, Dec. 9, 1920).

The fats in the lungs contain both vitamin A and antirachitic vitamins which fix calcium in the system. H. Roger, L. Binet and M. Vagliano (*C. r. Soc. de biol.*, July 11, 1924).

Calcium and phosphorus retention in infants fed quickly boiled milk mixtures proved considerably greater than when the milk mixtures were pasteurized. The longer heat treatment of milk causes decreased availability of the phosphorus and calcium. A baby fed pasteurized milk over a long period receives too little calcium for his growth requirements. A. L. Daniels and G. Stearns (*Jour. of Biol. Chem.*, Aug., 1924).

The effect of calcium in man is amphotropic, *i.e.*, exerted on both portions of the vegetative nervous system. At first there is a short period of marked vagus stimulation; this is followed by a less marked but more prolonged sympathetic stimulation, with rise of blood-sugar and blood-pressure, sometimes adrenalin mydriasis, etc. E. Barath (*Jour. of Nerv. and Ment. Dis.*, Sept., 1925).

Small doses of soluble calcium salts have been found to increase the energy of the exposed heart, and it is believed that calcium is essential to the dynamism of this organ. Small doses do increase the contractile energy of the myocardium, while large doses increase the rate of its contractions, cardiac paralysis ensuing if the doses are sufficiently

large. Deficiency of calcium results in excitation of nervous structures, while excess of calcium is depressant to nervous functions. It antagonizes the effects of magnesium and sodium.

In the frog's heart diastolic relaxation is rendered slower and less complete by calcium, with final arrest in systolic contraction. Such substances as potassium chloride, narcotics and acids act oppositely in this respect. F. Haffner (*Arch. de cardiol. y hemat.*, May, 1924).

The writer found the cardiac contractions strengthened by calcium in the isolated heart of the dog and rabbit. Moderate amounts caused slowing of the rate through stimulation of the vagus center, while large amounts caused transient auriculo-ventricular dissociation. A rise of blood-pressure resulted from contraction of the peripheral vessels. L. Brull (*C. r. Soc. de biol.*, July 11, 1924).

Attention called to a close similarity in the action of calcium and that of digitalis in man. This similarity applies also to the seat of the action. Each agent enhances the action of the other. The digitalis effect is, however, more prolonged. E. Billigheimer (*Zeit. f. klin. Med.*, July 25, 1924).

The actual rôle fulfilled by calcium in all tissues is still to be determined.

A human being needs 1.5 Gm. (24 grains) of calcium per day in the first six months of life and from 0.9 to 1.1 Gm. (14 to 17 grains) after the fifth year. (Loeper and Boveri.)

Calcium salts have been used extensively to arrest hemorrhage on the plea that they increase the coagulability of the blood. This view has been challenged, but the occurrence of thrombosis among the untoward effects of calcium intoxication sufficiently indicates the imprudence of casting aside the coagulation theory.

Intramuscular injections of sodium oxalate into rabbits in doses of 0.18

and 0.2 Gm. ( $2\frac{3}{4}$  to 3 grains) proved invariably fatal. The symptoms consisted in excitation and tonic and clonic convulsions. When calcium chloride solution was given in sufficient amount 1 minute after the oxalate injection the animals survived. Gates (Jour. Exper. Med., Sept., 1918).

The fate of calcium in the body depends on the reaction of the blood. If the hydrogen ion concentration is raised, more calcium is kept in solution, while if it falls, calcium deposition results. Frequent variations of blood reaction lead to increased calcium content of the bones, but a prolonged increase of hydrogen ion concentration leads to a migration of calcium from the bones to the blood. Rickets and tetany are opposite in that the former is attended with acidosis and the latter with alkalosis. C. R. H. Rabl (Münch. med. Woch., Apr. 11, 1924).

Marked variations in the blood calcium on different days observed in some cases of functional neurosis and emotional disturbance, including depression, dementia precox, hysteria and acrocyanosis. F. Glaser (Med. Klin., Sept. 7, 1924).

**CALCIUM POISONING.**—The toxic phenomena as represented in experimental animals are spasms indicating the predilection of calcium for muscular elements, with special manifestations in the direction of the heart: Arrhythmia, intermittent pulse, gradual diminution of cardiac power, and finally paralysis of the organ. In man, however, large therapeutic doses may produce venous thrombosis, numbness and tingling of the extremities, tinnitus, and deafness.

Having under his care a married woman aged 40 years suffering from a leg ulcer which seemed to be due to deep varicosity of veins, the writer gave her 15 grains (1 Gm.) of calcium chloride three times a day. At the time he did not further examine her, as she was fully dressed. On the third

day of treatment the author was called to see her. She was complaining of numbness of the right side of the body and was cyanotic. The next day she was a little better, but still had the feeling of "pins and needles" in her right arm and leg. On the following day she had complete hemiplegia. There is no doubt on account of the slow onset that the lesion was due to cerebral thrombosis. Examination showed that the patient had a mitral lesion, and the author came to the conclusion that the calcium salts had something to do with the condition.

Joseph Stark (Lancet, June 22, 1907).

Any untoward effect of calcium salts when taken in excess is counteracted, according to Sir James Barr, by citric acid, 30 grains (2 Gm.) three times a day, which favors its elimination from the blood.

**THERAPEUTICS.**—*Calcium Lactate.*—Of all the calcium salts, this is the least irritating, perhaps the most rapidly absorbed and oxidized, freeing the base, and also the most agreeable to the taste.

A single large dose of calcium lactate in man influences the plasma values but little. Calcium chloride seems to be absorbed better and shows more consistent increases in the plasma values. E. H. Mason (Jour. of Biol. Chem., June, 1921).

Calcium chloride, lactate and glycerophosphates, when given by mouth to dogs in amounts equivalent to 0.2727 Gm. of CaO per kilo., are absorbed rapidly enough to increase definitely the serum calcium, whereas the relatively insoluble salts, such as the carbonate, in like quantity, are inconstant in this respect. Calcium lactate is preferable to the chloride, even though it must be given in greater bulk, for it is less irritating to the gastric mucosa. Hjort (Jour. of Biol. Chem., Oct., 1925).

We have seen that calcium is not given to supply a deficiency of lime

in the body in osseous diseases such as **osteomalacia** and **rachitis**, because these disorders are due to its defective assimilation by the bone. But there is reason to believe that *thyroid gland* favors calcium metabolism and that its simultaneous use will cause calcium to prove useful in these disorders. Calcium lactate 10 grains (0.6 Gm.) and thyroid gland 1 grain (0.065 Gm.), given in a capsule after each meal, may be tried. Fixation of calcium may also be promoted by codliver oil, sunlight, the ultra-violet ray, and parathyroid gland.

**Genu valgum** and **varum**, **flatfoot**, **delayed** or **non-union** in fractures, and even **arthritis** may result directly from calcium deficiency. If fresh, uncooked milk, orange juice, and in many cases, thyroid gland are administered, the difference in the results is often remarkable. Further, lime water should be added to all milk given. Peckham (Jour. Amer. Med. Assoc., Nov. 13, 1920).

Subcutaneous or intravenous administration of calcium was found to raise the blood calcium to normal and maintain it there for some time in adults in whom it had previously been low. By mouth, doses of soluble salts equivalent to 1 to 1.5 Gm. (15 to 23 grains) of calcium were required to cause even a temporary increase in the blood calcium. Of the inorganic salts, *calcium bicarbonate* was the most effective in raising the blood calcium. Of the organic salts, calcium lactate had no effect on blood calcium, while *calcium acetate* increased it slightly. A pure solution of calcium bicarbonate was found to increase the blood calcium by 50 per cent., while the same quantity of calcium carbonate in a mineral water increased it only about 10 per cent. W. H. Jansen (Deut. Arch. f. klin. Med., Oct., 1924).

Calcium salts are useful in **cardiac weakness**, but, as emphasized by Sir James Barr, these salts are contra-

indicated in mitral stenosis. They are contraindicated also when calcification of the arteries, especially the aorta, is probable, as in the aged. Drunkards and persons suffering from lead poisoning are also said to be unfavorably influenced by any preparation of calcium.

Calcium lactate has proven effective in **tetany**, especially the form due to surgical removal of the parathyroid glands. It may be given subcutaneously in 30-grain (2 Gm.) doses in saline solution, and the effect sustained by giving orally 10-grain (0.65 Gm.) doses in milk every four hours. Urgent cases have been controlled by an intravenous injection of a 5 per cent. solution, but this entails the danger of causing thrombosis.

The calcium lactate has also been recommended in the treatment of **epilepsy**. In 15-grain (1 Gm.) doses, three times a day, it may either be used to alternate with the bromides or in their stead where these depressing salts, as is often the case, are contraindicated. It has also been recommended in **puerperal eclampsia** to counteract convulsions. Halford administers 15 grains (1 Gm.) of the lactate every 4 hours until the symptoms abate.

Certain forms of **headache**, confined to the frontal region, with throbbing about the temples and occurring as a rule on awakening, ascribed by Luff to a "lymphatic" condition of the blood, are benefited by calcium. He administers 15 grains (1 Gm.) of the lactate one hour before meals.

G. W. Ross has given details as to this form of headache as follows: (1) It is present and most severe on waking and tends to lessen or to disappear in from one to six hours. (2) It is usually a dull, heavy ache

or a frontal or temporal throbbing; less often it is vertical, occipital, or unilateral; rarely it is neuralgic. (3) It is chronic and intractable, but may exhibit itself as the common occasional headache to which many are subject. (4) It is associated with a deficient coagulability of the blood. The subjects of this form of headache are usually of the lymphatic type. The expression is heavy and listless, the face is full and the eyes puffy, anemia is often present, and the whole bearing indicates mental and physical lassitude. Symptoms which are often associated with the headache are pain after eating, constipation, edema of face or extremities, dyspnea, chilblains or urticaria, and neuralgia. In the treatment, the lactate is given in a mixture containing 15 grains (1 Gm.) of this drug,  $\frac{1}{2}$  minim (0.03 c.c.) of tincture of capsicum, and 1 ounce (30 c.c.) of chloroform water, to be taken three times a day before meals. If the lactate cannot be obtained, the chloride may be substituted, 15 grains (1 Gm.) in 1 ounce (30 c.c.) of camphor water. Calcium lactate may be combined with bitters and with iron and strychnine, but not with alkalies or alkaline carbonates.

Calcium is a better base in **acidosis** than sodium, as the excess of sodium might be harmful, while an excess of calcium is not and will maintain the proper degree of alkalinity of the plasma. Meyers (Jour. Amer. Med. Assoc., Mar. 6, 1920).

The lactate is also used in the treatment of **edema** of the lower extremities.

It is serviceable in **hemophilia** and **purpura** and the various forms of **hemorrhage**, *viz.*, **hemoptysis**, a predilection to **epistaxis** when not due to mitral disease, **hematemesis**, and **intestinal hemorrhage**. Ringer cautioned against the too prolonged use of calcium in hemorrhagic disorders on the plea that, otherwise, opposite effects were produced. He advocated an intermission of a few days every three or four days. In **acute hemorrhage**, however, as much as 60 grains (4 Gm.) have been given at once to

obtain prompt results. Simpson has recommended pre-operative use of calcium to prevent hemorrhage after tonsil and adenoid operations.

**Antepartum hemorrhage** is the cause of 15 per cent. of infantile deaths. There are many cases in which it can be controlled, *viz.*, those in which placental separation occurs owing to the condition of the blood. In these cases, to avoid repetition of the accident in subsequent pregnancies, calcium should be given from the beginning of each pregnancy. **Dysmenorrhea**, unless due to some developmental anomaly, displacement or new growth, will usually be relieved by a course of calcium, which should be continued for some months. S. H. Hall (Med. Press and Circ., June 3, 1925).

Intravenous injections of calcium salts in **tuberculous conditions** have been warmly recommended.

In 250 **tuberculous** patients given intravenous injections of calcium chloride, marked improvement in the symptoms was noted, including reduction of fever. The writer gives series of 20 injections daily or on alternate days, with intermissions of a week or 2. In **hemoptysis** he injects 5 c.c. (80 minims) of a 10 per cent. solution every 8 hours. Moendl (Zeitschr. f. Tuberk., Nov., 1921).

In **rebellious diarrhea** among the **tuberculous** (24 cases), **dysenteriform diarrhea** (12 cases), **vomiting in tuberculosis** (30 cases), and **hemoptysis** (2 cases), the writer induced a hemoclastic shock by injecting intravenously 2 to 4 c.c. ( $\frac{1}{2}$  to 1 dram) of a 50 per cent. solution of calcium chloride. The diarrhea, vomiting, and hemoptysis were checked in all cases, except 3 of vomiting. The reaction from such injections consists of a feeling of heat lasting 1 minute only. Pellé (Bull. et mém. de la Soc. méd. des hôp. de Paris, Feb. 10, 1922).

Certain cutaneous disorders, especially those of a pruriginous type, are

sometimes favorably influenced by calcium. **Urticaria, erythema, chilblains** with predilection to cold hands and feet, **boils**, and **offensive perspiration** often yield to the lactate. Bettmann obtained good results from a 5 per cent. solution of calcium lactate, 1 or 2 tablespoonfuls before each meal for 3 or 4 weeks, in **purpura, urticaria, senile pruritus**, and **herpes gestationis**. Various conditions related to **anaphylaxis**, including **bronchial asthma**, are sometimes relieved by calcium.

A relationship of calcium to sympathetic excitability pointed out. Injection of adrenalin 2 hours after injection of 3 to 5 c.c. of 10 per cent. calcium chloride solution was followed by a very rapid ascent and descent of blood-pressure. The immediate action of calcium is useful to increase sympathetic excitability, *i.e.*, in cases with evidences of vagotonia, as in **bronchial asthma**. The injections must be given every day or 2 to keep up the effect. Dresel and Jakobovits (Berl. klin. Woch., Apr. 8, 1922).

A stimulating effect of calcium on sympathetic nerve action accounts for its value not only in **asthma** but also in **intestinal tuberculosis, hay fever, acute rhinitis, serum disease**, and other conditions attended with excessive parasympathetic irritability. In a case of **anaphylaxis** due to injection of horse serum, intravenous injection of 5 c.c. (80 minims) of a 5 per cent. solution of calcium chloride brought relief. F. M. Pottenger (Amer. Jour. Med. Sci. Feb., 1924).

Favorable effects obtained from calcium in **anaphylactic shock** and various vagotonic states such as **nervous hyperacidity, vagotonic diarrhea, membranous enteritis**, and **chronic diarrhea following dysentery**. In **premenstrual pains** not due to local pathologic conditions, calcium proves useful, as also in **urticaria**, excessive **skin reactions to drugs or light**, and **chilblains**. In **tuberculosis** it is serviceable for the

palliation of **nightsweats, hemoptysis** and a persistent **subfebrile temperature**. It is also an antidote in **poisoning by arsenic, arsphenamin, oxalic acid, quinidine or cocaine**. R. Kaewel (Zeit. f. klin. Med., May 15, 1924).

In **asthma**, the giving of 1 tablespoonful of 5 per cent. calcium chloride solution every 2 hours is very useful. For intravenous injection of calcium the author uses a 10 per cent. solution of the crystallized salt. Occasionally **anorexia, constipation** and **vomiting** occur as untoward results of calcium treatment. K. Blühdorn (Klin. Woch., July 8, 1924).

**Calcium Chloride.**—This salt is preferred by some for the treatment of **cardiac disorders** of adynamic type. **Heart-failure** in infectious diseases in which this complication is apt to occur, such as **pneumonia, influenza, typhoid fever**, is efficiently counteracted with small doses frequently repeated. Brunton gave calcium chloride in doses of from 5 to 10 grains (0.3 to 0.6 Gm.) dissolved in water, every 4 hours, with excellent results in impending cardiac failure in **pneumonia**. The disagreeable taste of the salt was covered by 1 minim (0.06 c.c.) of the elixir of saccharin, containing  $\frac{1}{20}$  grain (0.0032 Gm.) of saccharin, for each 10 grains (0.6 Gm.).

Calcium salts, administered intravenously while digitalis is being given by mouth, appear to accelerate the action of the digitalis, at the same time antagonizing its secondary effects, *vis.*, digestive disturbances and undue vagus excitation. The dose, as employed by Singer, is 1 c.c. (16 minims) of 10 per cent. calcium chloride solution. Cheinisse (Presse méd., Jan. 28, 1922).

The clinical effects of intravenous injection of 10 c.c. of a 5 per cent. solution of calcium chloride are these: At an injection rate of 4 to 5 minutes for the 10 c.c., a slight facial flush is noted and the patient is conscious of a feeling of warmth more pronounced in the

face and in and over the abdomen. The blood-pressure rises 5 to 10 mm. Hg, but usually returns to normal within 30 minutes. The pulse-rate in asthmatics may drop 10 to 20, and remain at the lower rate for a short time. Upon more rapid injection the patient complains of a feeling of intense heat in the skin and breaks out in a profuse perspiration. There is a feeling of constriction in the throat and nausea, persisting for upward of 30 minutes; also a burning in the rectum. One patient developed aphonia, lasting for a few minutes. F. M. Pottenger (*Amer. Jour. Med. Sci.*, Feb., 1924).

Intravenous injection of 5 to 10 c.c. (80 to 160 minims) of a 10 per cent. solution of calcium chloride is capable of overcoming various arrhythmias, such as **premature contractions, paroxysmal tachycardia** and even **auricular fibrillation**. The attendant subjective symptoms are simultaneously relieved. The drug seems to be an actual heart-tonic. Petzetakis (*C. r. Soc. de biol.*, Aug. 12, 1924).

The other indications of calcium chloride are similar to those of calcium lactate. It may prove useful to oppose **chloride retention**, and has sometimes proven effective as diuretic in cases in which all other agents had failed.

In a case of marked **edema** refractory to ordinary diuretics, a rapid reduction of weight by 11 kilograms occurred upon administration of calcium chloride in large amount by the mouth. In the course of 5 or 6 days from 11 to 22 Gm. (165 to 330 grains) of the salt were given in various cases. In **hepatic cirrhosis, ascites** likewise subsided under calcium in 3 cases. Blum, Aubel and Hausknecht (*Bull. de la Soc. méd. des hôp. de Paris*, Nov. 25, 1921).

In cases of **inflammatory effusions** of the serous membranes, a low salt diet and large doses of calcium chloride cause the effusions to be absorbed, sometimes rapidly. In some acute

cases the inflammation was entirely controlled in 24 hours.

The crystallized and anhydrous salts are so hygroscopic that they always contain a variable proportion of water. The author prefers, therefore, to use the dry granulated salt which keeps perfectly in tightly closed flasks. The dose is at least 15 Gm. ( $\frac{1}{2}$  ounce), sometimes increased up to 30 Gm. (1 ounce) a day. A mixture of equal parts of the salt and soluble starch, with addition of water and syrup of lemon, is better for delicate stomachs. L. Blum (*Presse méd.*, Mar. 15, 1922).

In 2 cases of **nephritis with edema**, diuresis and loss of edema were seen under calcium treatment. Study of inorganic ions during the diuresis showed a positive balance of calcium and a negative balance of chlorine and sodium. Upon ingestion of calcium chloride, calcium is eliminated by the bowel and chlorine by the kidney. In certain cases, sodium (becoming attached to the absorbed chlorine) is discharged in large amounts, water being thus made available for elimination. The first case was one of sub-acute glomerular nephritis with extreme generalized edema of 9 months' standing in a man of 22 years. In conjunction with other treatment, calcium chloride was given by mouth in periods of 7, 10 and 9 days, and in doses of 18 or 10 Gm. (280 or 154 grains) a day, with the result that the weight was reduced from 92.7 to 55.4 kilos. in 65 days. The daily output of urine rose at times as high as 2200 c.c. The second was a less severe case in which 10 Gm. of calcium chloride for 4 days caused a sustained diuresis and disappearance of edema. At the end of the diuresis both patients had normal renal function. The drug was administered in capsules. N. M. Keith, C. W. Barrier and M. Wheelan (*Jour. Amer. Med. Assoc.* Aug. 30, 1924).

Calcium chloride has been recommended to prevent antitoxin rashes, but the evidence available regarding this practice is not altogether convincing

**Calcium Hypophosphite.**—This salt is thought by some observers to be one of the most readily assimilated of the series, particularly in **rachitis** and **osteomalacia**. It has been given with averred success in **pulmonary tuberculosis** to favor calcification of the tubercles and also in **neurasthenia** to enhance nerve nutrition. It is given in 5- to 10- grain (0.3 to 0.6 Gm.) doses three times a day, omitting the remedy a few days at short intervals.

**Calcium Hydroxide Solution (Lime Water).**—This valuable preparation is used mainly as a potent antidote in **arsenical poisoning**, and also in the treatment of **dysentery**, **infantile diarrhea**, owing to its antacid and mildly astringent properties. It is also employed to counteract vomiting; sips of a mixture of equal parts of lime water and milk will often arrest this symptom when other remedies fail. It is often added to the milk given to infants to prevent curdling and thus facilitate its digestion. Possessing as it does the property of dissolving mucus, it is used in **diphtheria**, **pseudomembranous croup**, **fibrinous bronchitis** to facilitate the elimination of the false membrane. It has been found efficient in **diabetes insipidus**.

**Calcium Carbonate.**—The reaction of this salt is similar to that of the above. It is often preferred because it may be prescribed in small bulk, powders for example, which may be added to water, milk, etc., to insure free dilution—a wise precaution to avoid irritation of the gastrointestinal mucous membrane.

**Prepared Chalk or Chalk Mixture.**—This preparation was formerly used extensively in the treatment of **infantile** and **choleraic diarrhea**, Mukherji

(1918), in bacteriologic experiments, found lime water, if used in sufficient amount, inimical to cholera vibrios.

**LOCAL USES.**—Several of the calcium preparations have been used locally to advantage.

Equal parts of lime water and olive oil form a thick fluid (*carron oil*) which is of great value in the treatment of recent **burns**. It affords a covering which protects the injury from the air and thus reduces the pain, while promoting resolution.

Lime water alone is also advantageous as a local application for pruriginous skin disorders in conjunction with the internal use of calcium lactate. Especially is this the case in **urticaria**, **erythema**, **chilblains**, and **offensive perspiration** of the axillæ and feet.

Calcium sulphate (*gypsum*) forms an efficient dusting powder for the eruption of **small-pox**. It reduces the tendency to ulceration, relieves the itching, and acts as a deodorant. The same properties render it useful in **leg ulcer**.

Chlorinated lime (*bleaching powder*) yields on exposure to the air hypochlorous acid. This in turn breaks up, yielding its chlorine. It is very active, therefore, as a disinfecting and deodorizing agent for cesspools and the excretions of invalids especially. A solution of 1 part to 100 parts of water destroys the pathogenic organisms of urine, fecal discharges, sputum, etc., and is preferred to other disinfectants owing to the fact that it does not injure bedding, clothing, etc., though of course bleaching these articles if their colors are not fast. Freely diluted it is also useful in the local treatment of **ulcers**.

One of the more recent uses of a

calcium salt is to replace the bismuth in pastes for the treatment of **sinuses** and **deep ulcerations** and thus avoid its untoward effects (see Bismuth, this volume). Equal parts of calcium carbonate and petrolatum were found by Mitchell equally effective.

Crude calcium sulphide, besides its use as a depilatory, has been recommended internally in 1-grain doses in boils, suppurative processes generally and acute infectious diseases. Its efficiency is doubtful (Sollmann).

Calcium carbide has been advocated as a caustic for inoperable cancer.

The writer has used calcium carbide extensively as a caustic in the treatment of various superficial lesions, and prefers it to all other substances for this purpose. In contact with water, the carbide decomposes into calcium oxide (lime) and acetylene gas. The chief advantages he claims for it are that it does not attack healthy skin if the latter be kept dry, affecting only diseased areas which present a moist surface; that it causes but little pain; that it is strongly hemostatic and antiseptic, and that it is non-toxic. L. Desguin (Gaz. méd. belge, May 25, 1911).

Chlorinated lime has been extensively used for the **sterilization of drinking water**, particularly for troops. This action is attributed to the chlorine the salt contains.

In a study of the limitations of chloride of lime tablets for the sterilization of drinking water by troops, the writer ascertained that their efficiency depended not only on the kind of the germ, but also on its resistance to the action of germicides. The cholera spirilla are destroyed very readily. Some of the other micro-organisms require a much longer contact. In the presence of considerable organic matter in the water, a larger quantity of chlorine is required. Also, the amount of

chlorine will be influenced by the reaction of the water. In the author's experiments, 2 milligrams ( $\frac{1}{2}$  gr.) of chlorine to the liter (quart) of water killed the cholera spirilla in 10 minutes; the typhoid bacilli were destroyed in 2 hours and 40 minutes; the dysentery bacilli in 2 hours and 45 minutes; and the colon bacilli in 3 hours and 5 minutes. Archipiantz (Roussky Vrach, Apr. 30, 1916).

The city of Rheims has been using for 3 years a method of water sterilization instituted by Bunau-Varilla during the battle of Verdun, and which is based on the use of extremely small amounts of sodium hypochlorite, corresponding to 0.0001 Gm. of free chlorine per liter of water. With this minute amount, no taste is imparted to the water. Experience has shown the efficacy of this procedure, which is available for the sterilization of water wherever sodium hypochlorite is obtainable. Where such is not the case, sodium chloramine 0.005 to 0.01 Gm. per liter, may be used. Techoueyres and Pillement (Bull. de l'Acad. de méd., Mar. 30, 1926).

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

**CALOMEL.** See MERCURY.

**CALUMBA** (or *columbo*) consists of the dried root of *Jatcorrhiza palmata* (natural order Menispermaceæ), a plant of the southeastern coast of Africa and of the East Indies. It has a slight odor and an aromatic, very bitter taste, and contains the alkaloid *berberine*, a bitter, neutral principle known as *columbin* ( $C_{21}H_{22}O_7$ ), *columbic acid* ( $C_{21}H_{22}O_8 + H_2O$ ), *cholesterin* and *mucilage*, but no tannin.

**PREPARATIONS AND DOSE.**—*Calumba*, U. S. P. (calumba root). Dose, 15 grains (1 Gm.).

*Tinctura calumbæ*, U. S. P. (tincture of calumba). Dose,  $\frac{1}{2}$  to 2 fluidrams (2 to 8 c.c.).

*Fluidextractum calumbæ*, N. F. (fluidextract of calumba). Dose, 15 to 60 minims (1 to 4 c.c.).



The British Pharmacopœia recognizes also:—

*Infusum calumbæ* (infusion of calumbæ).

Dose,  $\frac{1}{2}$  to 1 fluidounce (16 to 32 c.c.).

**THERAPEUTIC USES.**—Calumbæ is one of the best of the simple bitters, having no astringency, but on the other hand, through its bitter taste, stimulating the flow of saliva and gastric juice and promoting gastric circulation, thus increasing the appetite and improving digestion. Though it is one of the least irritating of the gastric tonics, its long-continued use may induce a catarrh of the stomach or diarrhea.

Calumbæ, with quassia and chirata, is peculiar among the bitter tonics in containing no tannic acid; it may therefore be prescribed in combination with iron without causing precipitation, as in the following:—

*R. Fluidextracti calumbæ.* f3iv (16 c.c.).

*Tincturæ ferri citro-*

*chloridi* (N. F.) ... f3ij (8 c.c.).

*Elixiris aromatici,*

q. s. ad ..... f3iij (100 c.c.).

M. Sig.: One teaspoonful an hour after meals.

The drug is very useful in **atonic dyspepsia**, with discomfort after meals, and in the period of **convalescence** from acute diseases to promote appetite and digestion. Pouchet recommends the following preparation containing calumbæ as a bitter tonic:—

*R. Extract of calumbæ,*

*Extract of quassia,*

of each ..... 2.5 Gm. (gr. xl).

*Malaga (or Ma-*

*deira) wine* ..... 500.0 Gm. (Oj).

M. Sig.: One or two tablespoonfuls one-half hour before each of the two principal meals.

In **diarrhea**, **dysentery**, and **cholera morbus**, calumbæ has been found valuable by some. It may also be tried in the **vomiting of pregnancy** and in **seasickness**. In **pulmonary tuberculosis** calumbæ is useful to stimulate the appetite. Schulz used it successfully in the diarrhea of phthisis, administering the tincture in doses of 40 minims to 3 drams (2.5 to 12 c.c.) once or twice a day.

W.

**CALX.** See **CALCIUM**.

**CAMBOGIA.** See **GAMBOGE**.

**CAMP FEVER.** See **TYPHUS**.

**CAMPHOR.**—Camphor is a tough, crystalline, white, translucent gum obtained mainly from the *Cinnamomum camphora* (Linné), or camphor laurel, indigenous in eastern and southeastern Asia. It is a dextrogyrate modification of the saturated ketone,  $C_9H_{16}CO$ , purified by sublimation. It evaporates gradually on exposure to the air at ordinary temperatures, and sublimes when moderately heated without leaving a residue. It should be kept in a cool place in well-stoppered bottles.

Camphor has a penetrating aromatic odor and a pungent, somewhat bitter taste, which leaves in the mouth a feeling of freshness or coolness. It is sparingly soluble in water, but readily so in alcohol, ether, chloroform, carbon disulphide, petroleum benzine, and in fixed and volatile oils. It cannot be reduced to powder in its normal state, but is readily pulverizable when a little alcohol, ether, or chloroform is added to it.

#### PREPARATIONS AND DOSE.

—The official preparations of camphor and their doses are as follows:—

*Camphora* (camphor), 2 to 10 grains (0.12 to 0.6 Gm.). It should be given in the form of pills or in capsules.

*Aqua camphoræ* (camphor water), which contains 0.2 per cent. of camphor. Dose,  $\frac{1}{4}$  to 2 fluidounces (8 to 30 c.c.).

*Linimentum camphoræ* (camphorated oil, or camphor liniment), composed of camphor, 20 parts, and cottonseed oil, 80 parts. For local use.

*Linimentum saponis* (soap liniment), composed of camphor, 4.5 parts; soap,

6 parts; oil of rosemary, 1 part, and alcohol, 100 parts. For external use.

*Spiritus camphoræ* (spirit of camphor), composed of camphor, 10 parts; alcohol, 100 parts. Dose, 10 to 30 minims (0.65 to 2.0 Gm.).

*Tinctura opii camphorata* (camphorated tincture of opium, or paregoric), composed of camphor, powdered opium, benzoic acid, oil of anise, of each, 4 parts; glycerin, 40 parts; diluted alcohol, enough to make 1000 parts. Each fluidram (4 Gm.) of this preparation contains  $\frac{1}{4}$  grain (0.016 Gm.) of powdered opium and  $\frac{1}{4}$  grain (0.016 Gm.) of camphor. Dose, 1 to 4 fluidrams (4 to 15 c.c.).

No longer official is *monobromated camphor*, a substitution compound of camphor ( $C_{10}H_{15}BrO$ ), prepared by heating camphor and bromine, dissolving in benzene, and crystallizing from hot alcohol. It occurs in the form of colorless scales or needles, having a camphor-like odor and taste. It differs from camphor, however, in not being volatile. Its solubilities are the same as those of camphor. Dose, 2 to 5 grains (0.12 to 0.3 Gm.).

Also unofficial is *camphoric acid*, a dibasic organic acid,  $C_8H_{14}(COOH)_2$ , obtained by the oxidation of camphor, occurring as colorless crystals, with a faint aromatic odor and a slight camphor-like taste. It is soluble in 125 parts of water and readily in alcohol and fatty oils. Dose, 10 to 30 grains (0.6 to 2 Gm.), administered preferably in capsules.

Besides the above preparations of camphor, there are several that are used to advantage. Several of these we owe to the fact that, when camphor is triturated in about molecular proportions with menthol, thymol, phenol, or chloral hydrate, syrupy

fluids termed *camphor-menthol*, *camphor-thymol*, *camphor-phenol* and *camphor-chloral* are obtained, which are mainly employed locally.

#### PHYSIOLOGICAL ACTION.—

Camphor in small doses seems to exert a mildly sedative action on the nervous system, while large doses stimulate the latter, the cerebrum and medulla especially, causing psychic exaltation, visions, delirium, hysterical paroxysms, and even epileptiform convulsions.

Camphor, as well as thymol and menthol, depress the isolated heart of both the frog and rabbit directly, but dilate the coronary vessels. In anesthetized animals camphor, however given, does not cause a rise of blood-pressure if the dose administered to these animals is not sufficient to cause convulsions. R. St. A. Heathcote (Jour. of Pharm. and Exp. Ther., Apr., 1923).

Camphor paralyzes impulse formation and conduction in frog hearts, and in large doses stimulates the latent automatism. The favorable effects of camphor in strophanthin and aconitine poisoning are due to its paralyzing action on the abnormally irritated heart muscle. Nakazawa (Tohoku Jour. of Exp. Med., July 30, 1923).

Camphor has also been credited with stimulating the heart and increasing the *vis a tergo* motion of the blood, but this action becomes more especially manifest when the cardiac action is depressed. Though causing a brief primary vasoconstriction through stimulation of the vasomotor center, it tends to dilate the peripheral blood-vessels. According to Liebmann this dilator effect is exerted first on the pulmonary, then on the systemic vessels. On the whole, however, the effects of camphor on the blood-pressure are variable.

Camphor exercises a favorable effect upon the heart muscle, when it is poisoned by chloral, muscarine, or strychnine, but the authors consider it unreliable as a cardiac stimulant. Heard and Brooks (*Amer. Jour. Med. Sci.*, Feb., 1913).

Broken compensation in valvular disease of the heart, with cardiac failure, is not suited to camphor, but while we may not be able to explain satisfactorily why it acts as a cardiac stimulant, the fact remains that such is the case when the drug is employed in the proper sort of cases. Hare (*Therap. Gaz.*, Apr., 1913).

The long continued administration of camphor to rabbits did not seem to impair in any way the functioning or the structure of the heart, but rather to increase its functional capacity. But it did not render the heart more resistant to phosphorus poisoning or to diphtheria toxin, and did not aid in throwing off the effect of ether. The writer found small doses of camphor very useful in keeping up the tone of the heart with chronic myocarditis. Sigerist (*Corresp. blatt. f. schweizer Aerzte*, Dec. 22, 1917).

Whether the effect be exerted upon the nervous system, and through the circulatory variations it produces in the latter, the fact remains that camphor allays, in small therapeutic doses, both nervous excitement and muscular spasm, while promoting a general sensation of warmth. The secretions are not affected by the drug with the exception of the sweat, owing doubtless to the dilatation of the cutaneous blood-vessels. The temperature is not sensibly influenced unless fever be present, when it tends to lower it somewhat. While the respiratory function is enhanced by therapeutic doses, owing to their stimulating action on the respiratory center, toxic doses depress the latter. Its great volatility renders the action

of camphor in small doses ephemeral; it is advisable, therefore, to administer it preferably in small, but frequently repeated doses.

**Local Action.**—Locally applied, camphor causes slight irritation, a sensation of freshness due to its evaporation, and partial anesthesia. Taken orally in small doses it causes a feeling of warmth and in large doses marked irritation, but the gastric mucosa is particularly sensitive to its action and ulceration has been known to occur. Camphor is slightly antiseptic. When administered hypodermically it causes pain.

**Absorption.**—Camphor is absorbed with fair promptness, but irregularly, according to the oxidizing power of the fluids with which it comes into contact. It combines in part in the liver with glycuronic acid to form camphoglycuronic acid, a harmless combination, and is also partly exhaled through the lungs and eliminated by the skin, the excess remaining in the body, causing therapeutic or toxic phenomena according to the quantity taken.

Part of the camphor enters into a harmless combination with glycuronic acid in the body and part is exhaled through the lungs. The fraction remaining is what exerts the therapeutic action on the vascular system. From his research, the writer concludes that the fatal dose is about 1 Gm. (15 grains) to the pound of body weight of a healthy human being or animal. The toxic dose is a third less. These proportions are less in persons who at the moment of the injection are not able to form or have not already on hand the amount of glycuronic acid necessary to combine with the camphor to form the harmless camphoglycuronic compound. As glycuronic acid is a product of the oxidation of grape-

sugar, when there is a lack of either grape-sugar or of oxygen, there will be correspondingly less glycuronic acid, and in such case a smaller proportion of camphor will have a toxic action. This assumption was confirmed by his experiences with twenty out of thirty-five rabbits on which he experimented. Healthy rabbits bore intravenous injection of 0.08 Gm. ( $1\frac{1}{4}$  grain) of camphor without apparent injury, but this amount proved rapidly fatal if they had been fasting, and thus deprived of grape-sugar, for from six to nine days previously. Similar experiments in which the animals were deprived of oxygen, instead of the grape-sugar, proved equally fatal when the camphor was injected, the animals succumbing after injection of 0.02 or 0.04 Gm. ( $\frac{1}{4}$  or  $\frac{3}{8}$  grain) of camphor, from one-fourth to one-half the previously tolerated dose. These findings were corroborated by the effect of glycuronic acid injected at the same time with the camphor. Animals thus injected showed little, if any, disturbances and were soon as lively as ever, while the controls all died. These experiences warn physicians to be cautious in administering camphor to patients whose carbohydrate metabolism is defective, such as cachectic persons or those in inanition, or in severe cases of diabetes or chloral poisoning. On the other hand, great caution is necessary in administering camphor to persons with a deficient supply of oxygen, as in carbon dioxide intoxication, in severe cardiac defects, in advanced bilateral pneumonia, in severe sepsis, and to eclamptics. In eclampsia (as in the case reported by the writer) and psychic excitement, camphor is further contraindicated on account of the fact that its base of action is in the central nervous system. K. Happich (Jour. Amer. Med. Assoc., from *Centralbl. f. Gynäk.*, Dec. 30, 1905).

**POISONING.**—Although the textbooks hardly refer to the fact, poison-

ing by camphor is by no means infrequent, even under the influence of comparatively small doses, the sensitiveness to its action varying considerably in different individuals, weak subjects being especially vulnerable. While 30 grains (2 Gm.) will cause threatening phenomena in the strong, 6 to 7 grains (0.4 to 0.5 Gm.) will suffice to do so in a weak or old adult.

The use of large doses of camphor as a bactericide and analeptic is a dangerous practice. Some surgeons have thrown as much as 50 or 100 c.c. (1.7 or 3.4 ounces) of camphor oil into the peritoneal cavity after a laparotomy, and the belief has been freely expressed that camphor can do no harm. Even years ago Ziemssen stated that this substance "has no maximum dose." Nevertheless camphor is quite toxic to small animals, to the amount of 1 cg.— $\frac{1}{16}$  grain (3 cg.— $\frac{1}{2}$  grain—will kill a rabbit). Given as vapor and respired by the animal, the toxicity is notably increased. The danger for mankind lies in giving large doses to a badly weakened subject. The overaction of camphor is expressed ordinarily by marked slowing of pulse and tendency to collapse. Happich (*Münch. med. Woch.*, March 19, 26, and April 2, 1912).

Case observed by the writer in which a baby of 18 months was given a brimming teaspoonful of camphorated oil by mistake, containing from 14 to 15 grains (0.91 to 1 Gm.) of camphor, without causing any symptoms of note. D. J. Milton Miller (*Jour. Amer. Med. Assoc.*, Aug. 15, 1914).

The writer describes 5 cases in which epileptiform seizures were caused. The camphor had been prescribed for gonorrheal urethritis but the patients took the doses too often. In the fifth patient the camphor had been prescribed to relieve a painful cystitis, 1.5 gram (23 gr.) in the course of 2 hours. The convulsion occurred the following morning.

There was only 1 seizure in each case, but all described it as resembling a typical epileptic seizure. The camphor had been given with hexamethylenamine in all. Austregesillo (*Semana Medica*, Mar. 4, 1915).

Death followed ingestion of 1 dram (4 Gm.) of camphorated oil by a baby 3 weeks old. The maximum temperature was 100.6° F. (38.1° C.) and the child only showed signs of bronchitis, which had been diagnosed before the camphorated oil was administered. After 43 hours the child died very suddenly in a cyanotic attack. Haas (*Amer. Jour. of Obstet.*, June, 1916).

A sensation of heaviness about the head, developing into a violent headache and vertigo in some cases; marked weakness, and a tendency to collapse initiate the toxic phenomena. Nausea and vomiting are often observed. A sensation of burning in the mouth, throat, and stomach, with eructations which give off an odor of camphor, are valuable diagnostic signs when they occur, but this is not always the case. The breath may also smell strongly of camphor. Delirium is a common symptom which may be observed when therapeutic doses as small as  $\frac{3}{4}$  grain (0.05 Gm.) are administered in the course of infectious diseases.

Two cases in which marked delirium followed 9 and 9 $\frac{3}{4}$  doses. The effect on the hearts had been very satisfactory, but an intractable delirium had set in in both cases. At first this was not ascribed to the drug, which was continued. Bromine was given to quiet the condition, without success. After three days it occurred to the writer that the camphor might be responsible for the delirium; he therefore discontinued the powder and gave bromide alone. The untoward symptom disappeared promptly. F. Bohlen (*Deut. med. Woch.*, May 16, 1901).

The pulse, full and strong at first, gradually weakens and becomes more rapid until finally it is uncountable. The temperature follows a somewhat similar curve, hypothermia corresponding with an advanced stage of poisoning, attended also by coldness of the extremities, being usually present. Free sweating starts early, but may continue throughout the advanced stage. The face, flushed at first, becomes cyanosed; these phenomena are attended with more or less dyspnea and rapid or irregular and sometimes stertorous breathing. The pupils are moderately and equally dilated; but later the eyes may become staring, with loss of the conjunctival reflex.

Case of camphor poisoning in a Hindu married woman aged 28 who had an attack of choleraic diarrhea in the month of July. She had copious stools and vomiting. A bottle of Rubin's spirits of camphor was administered by someone in the house in three doses. The diarrhea was stopped, but the patient began to vomit, and experienced a terrible burning pain in the stomach and the throat.

The author saw the patient three days after the accident. The patient still complained of pain in the throat and stomach, and vomiting was still present. She was anemic and pale; conjunctiva was bloodless. There was complete anorexia and intense thirst. She was helpless, though quite restless, and had a low muttering delirium, a vague look, and was evidently in anguish.

There was fever at first, palpitations, and occasional symptoms of suffocation. The pulse was slow and feeble. The lungs were quite free. The bowels were constipated and the urine scanty. She was sleepless for some days.

She was given a bromide mixture with belladonna. She slept well, but

delirium was not abated at first. Excepting whey and barley water, no solid food was given for four or five days until the burning sensation in the throat and stomach passed away. On the fourth day the writer gave her a gastric sedative to allay the pain and irritation. She was now given milk and soup daily and gradually rallied. Roy (*Calcutta Med. Jour.*, Aug., 1911).

The nervous phenomena are, as a rule, very marked. The delirium referred to above may be preceded or followed by hysterical excitement, or it may be accompanied by a sensation of swinging or lifting in the air. In most cases, however, a period of excitement is followed by unconsciousness or epileptiform convulsions. The latter are often typical, being preceded by a loud outcry and accompanied by frothing at the mouth, biting of the tongue, involuntary urination, etc., the scene often ending in coma and death.

Case in a man who had taken a dose from a bottle which contained only camphor and alcohol. The patient was unable to stand. Respirations 60 to 70 per minute; pulse 130 and weak, but regular. Face bore an anxious expression and was very pale; lips cyanotic; pupils practically normal and equally dilated. Cold perspiration on forehead and face; extremities cold and trembling. Patient was thoroughly conscious, but was unable to speak above a whisper, and then but a few words and with much difficulty. There was no pain at all, at any time, but he complained of a tingling and numbness of the whole body, beginning in the toes and extending upward, and for the time being a paralysis of the legs. There was a feeling of swinging in the air and a sense of impending death from inability to breathe. It occurred to the writer that he might have a case either of wood alcohol or camphor poisoning, but on smelling

the bottle he decided it must be camphor.

Immediately  $\frac{1}{250}$  grain (0.0002 Gm.) of **glonoin** was given by the mouth and  $\frac{1}{50}$  grain (0.002 Gm.) of **strychnine nitrate** hypodermically. Within a very few minutes there was a cessation of difficult breathing, but it was soon followed by another wave-like attack which began in the feet, and swept up the limbs and arms to the back, and finally to the top of the head. Marked dyspnea accompanied each wave-like attack, which was increasing in frequency, duration, and severity until the glonoin and strychnine were given.

Shortly after giving the above, the writer gave a pint of warm water, to which a little salt had been added, to precipitate any camphor remaining in the stomach, and also to promote vomiting, the patient at this time being sufficiently recovered to object strenuously to the passage of the stomach-tube. The warm salt water produced free emesis. The vomited matter consisted of material resembling the precipitate formed by placing camphor in water and smelled strongly of camphor. Several pints of the **warm salt solution** were repeated and vomited until the stomach was apparently pretty well cleansed.

From this time on, the improvement was rapid, but there was slight dyspnea for a day or so, and from the continuance of a few doses of glonoin and strychnine no further attention was given. O. M. Rhodes (*Med. Fortnightly*, Aug. 25, 1906).

Case of poisoning by camphor liniment. An infant 1 year and 4 months old swallowed about half an ounce (15 Gm.) of the liniment. The *linimentum camphoræ* of the British Pharmacopœia contains camphor, in flowers, 1 part; olive oil, 4 parts; so that about 1 dram (4 Gm.) of solid camphor in solution was probably taken. Although the infant was promptly "turned over" and made to vomit, after an hour the symptoms began to develop. The eyes gradually became staring, she moaned,

and convulsions began. She was then given some salt and water, and vomiting occurred. When the writer saw her there were very marked convulsions, with irregular breathing, flushed face, and profuse perspiration; the pulse was rapid, the pupils were moderate and equal in size and inactive to light, and there was no conjunctival reflex. She was put in a hot bath, with cold cloths to the head. The stomach was washed out with warm water until quite clear of oil and *débris*, the washings being placed in four successive bowls. The first two contained food remains in small quantity, with a considerable amount of oil coating on the top, smelling distinctly of camphor. The last two showed the merest film of oil and did not smell. The pulse was about 200, temperature in rectum (taken twice) 106.4° F. (41.5° C.). Remedies seemed to have little or no effect. Chloral hydrate (3 grains—0.2 Gm.) by the rectum, small doses of potassium bromide by stomach-tube and by rectum, hot milk and water similarly given, and brandy were tried. While giving chloroform the fits were heralded by a flickering of the eyelids, the spasms spreading to the abdominal and back muscles and then to the extremities. There was usually at first conjugate deviation of the eyes and drawing of the mouth to the left, followed by the turning of the eyes and mouth to the right. On ceasing the chloroform the convulsions became more continuous, but were not so violent; the breathing was decidedly better. Later there was a slight return of conjunctival reflex. Soon collapse set in, and the infant died. Barker (Brit. Med. Jour., April 16, 1910).

Report of cases of eruptions due to camphor. A child debilitated by gastroenteritis developed an eruption when given injections of camphor in ether, which passed off when the camphor was stopped. Another child had a scarlatinoid rash upon treatment of pneumonia with camphor. An adult developed urticaria after injections of camphorated oil. Lambri (Policlin., July 6, 1925).

The urine is apt to be scanty and cloudy and may contain blood-corpuscles, red and white. No albumin is usually found.

No untoward effects usually follow recoveries, the exceptions being temporary paralysis, meningeal congestion, tingling and numbness, or soreness of the legs and abdomen.

Case of meningitis due to camphor poisoning in a child 2½ years of age who was found unconscious, covered with cold perspiration, and with an uncountable pulse. Six hours before, a teaspoonful of camphorated oil had been given in mistake for castor oil. Vomiting had been frequent. Potassium bromide was injected into the rectum. This controlled the convulsions. There was gradual improvement until the third day, when symptoms of meningitis developed. The case appeared to be almost hopeless, but under injections of caffeine there was slight improvement and a gradual recovery, with the exception of a paralysis of the right arm and leg. T. H. Walker (Lancet, Nov. 18, 1905).

Two cases of death from pulmonary fat embolism following intravenous injection of 1 and 5 c.c. of camphorated oil, illustrating that this procedure is not free from risk. The first case, receiving only 1 c.c., had a phlebitis following an operation for gall-stones, and received digitalis intravenously along with the camphorated oil. Fabricius-Moller (Ugeskr. f. Laeg., May 31, 1923).

Stress laid on the intolerance of cases of disease of the liver and bile passages for camphor. Such symptoms as vomiting, weakness, feeble pulse and dry tongue may result. The condition is ascribed to deficiency of glycuronic acid to combine with the camphor, on account of the hepatic disturbance. G. Sabatini (Policlin., Jan. 5, 1925).

**TREATMENT OF CAMPHOR POISONING.**—The first step is to empty the stomach as soon as pos-

sible by means of an **emetic** or, better, by washing out the organ with **warm saline solution**, which itself promotes emesis. **Sugar** has been recommended as an antidote on theoretical grounds.

Berkholz reported a case of camphor poisoning in a young woman who had taken about 15 Gm. ( $\frac{1}{2}$  ounce) of camphor suspended in water, probably to produce abortion. Two hours later a violent headache developed, with vomiting, convulsions, and later coma. The pulse was full and strong, and respiration rapid. Excitement increased until the patient became unconscious. The **stomach** was **washed out** several times and **chloral** and **bromide** were administered. After several days' illness she entirely recovered. The fatal dose of camphor is 2.5 to 7 Gm. (38 to 108 grains), and the writer attributed the recovery to the fact that the patient had eaten a hearty dinner composed largely of carbohydrates a short time after taking the poison. By this means there was formed in the intestine glycocamphoric acid, which is not poisonous. He recommends in camphor overdosage, therefore, that the patient be given large doses of **sugar** as an antidote.

In a case of bilateral *camphorated oil* tumors in the thighs, reduction of the tumors by one-half was obtained through **rest in bed** for 10 days and **ice applications**. Further reduction was secured with **mercurial ointment**. O. Cignozzi (Rif. med., July 16, 1923).

The influence of camphor on the nervous system, especially in view of the tendency to convulsions, renders the **bromides** and **chloral hydrate** of at least theoretical value; but the same plea would cause **strychnine** to be contraindicated, though generally used. The giving of alcohol or oils should be avoided, as they tend to enhance absorption.

**Chloroform** has also been used to check the convulsions, but the results obtained do not seem to warrant its administration.

**THERAPEUTICS.**—Camphor is much used as circulatory and respiratory stimulant in **collapse**, **heart-failure** where the myocardium is mainly at fault, and general **adynamia** due to abnormal vasodilation, as in **shock** and **exhaustion**. The most efficient mode of administration in emergency cases is 15 minims (1 c.c.) of a 10 per cent. solution in sterile olive oil hypodermically every fifteen minutes four times if needed, watching the patient closely, and ceasing the injections as soon as the patient is restored.

Camphorated oil has long been used in the asthenic stage of infections, the exanthemata, **scarlatina**, **measles**, **small-pox**, etc., and also in **pleuropneumonia**, **lobar pneumonia**, **pulmonary edema**, **infectious endocarditis**, **typhoid fever**, **influenza**, etc., owing mainly to the favorable reports of Huchard, Schilling, and others.

Later, Seibert pointed out the possibility that, in **pneumococcic infections** at least, camphorated oil exerted a direct destructive action upon the pathogenic organism. He found that it reduced the toxemia gradually until practically normal conditions were reached three or four days after the first injection. This favorable result and the absence of crisis occurred in every case. To the bactericidal action of camphor was attributed also the favorable results noted by Huchard, Schilling, Thassia, Alexander, and others.

In 21 cases of **pneumococcic pneumonia**, 12 c.c. (3 drams) of a 20 per cent. camphorated oil were injected every twelve hours in adults, and 6 c.c. ( $1\frac{1}{2}$  drams) in children (the youngest being 4 years of age), irrespective of the size and weight of the patient, the intensity of the toxemia, and the extent of the local process.



In 4 of the next 16 cases the limitations of this treatment were observed. A sudden rise of temperature in 2 patients on the second and third days of treatment, respectively, proved to be due to pneumococcic nephritis, promptly subdued by appropriate doses of hexamethylenamine, while the camphor injections were continued and resulted in speedy recovery. In 2 cases of severe **pleuropneumonia** from the onset (aged 13 and 28, respectively) the camphor reduced the general toxemia markedly, but did not prevent the accumulation of pus in the pleura, necessitating rib resection in the one on the fourth, and in the other on the eighth, day after the initial chill, pneumococci in pure culture being found in the exudate, and both patients recovering. The one death among the 37 cases of **pneumonia** so treated occurred in a man 68 years of age, weighing 200 pounds, with fatty heart and with pneumococcic invasion of both lower lobes.

The writer's observations have established the following facts: (1) That 10 c.c. ( $2\frac{1}{2}$  drams) of a 30 per cent. camphorated oil (equal to 36 grains—2.3 Gm.—of pure camphor) injected hypodermically to 100 pounds of human body weight every eight to twelve hours do not produce symptoms of poisoning; in fact, are harmless; (2) that much larger doses (to the body weight) in rabbits are equally well borne; (3) that these quantities of camphor materially assist in overcoming pneumococcic toxemia, and (4) that the earlier this treatment is resorted to the better the results. Seibert (Med. Record, April 20, 1912).

The addition of camphor to digitalis in the treatment of **pneumonia** has also been claimed to enhance the beneficial effects of the latter drug in this disease. Quisling, in particular, combines a 1 per cent. infusion of digitalis with an equal quantity of camphor emulsion of the following composition: Pulverized camphor, 1 part; mucilage of acacia, 40 parts;

distilled water, 159 parts. The combination is given in tablespoonful doses every hour during the first 12 hours, then every other hour.

Camphorated oil injections into the peritoneal cavity have been recommended by Höhne and Pfannenstiel to prevent **peritonitis** in laparotomy for severe infections. Such amounts as 50 c.c. ( $12\frac{1}{2}$  drams) have been introduced for this purpose.

The following formula is used by the writer in his surgical cases:—

*R Camphor* ..... 5ij (12 Gm.).

*Purified olive oil* .. 5ix (36 c.c.).

M.

After the camphor is dissolved the oil is filtered. Twenty c.c. (5 drams) are injected twice daily when the heart action is feeble. The results, even in grave **septicemia**, have been excellent, and the dose has been raised to 100 c.c. ( $3\frac{1}{2}$  ounces) daily without unfavorable symptoms. The camphor is rapidly eliminated through the lungs. P. Baudet (Province médicale, March 11, 1911).

A diversity of opinion exists as to the value of camphor as a circulatory stimulant. Fourteen patients with advanced congestive heart failure and 2 normal subjects were given intramuscular injections of camphor in oil in repeated small doses and single large doses, the total amount varying from 0.6 to 3 Gm. (9 to 45 grains). No evidence was obtained that the camphor had any action on the heart rate, respiration, blood-pressure, vital capacity, electrocardiogram, or general clinical condition. Subsequent administration of digitalis resulted, in 10 out of 12 of these patients, in prompt, definite improvement. H. M. Marvin and J. D. Soifer (Jour. Amer. Med. Assoc., July 12, 1924).

Various observers have advocated giving camphor intravenously, either in aqueous solution or in oil. The latter method does not seem altogether safe.

Intravenous injections of a saturated aqueous solution given, Ringer's saline solution being used as medium. The amount of camphor injected each time varies from 10 cg. ( $1\frac{1}{2}$  grains) in 75 c.c. ( $2\frac{1}{2}$  ounces) solution to 30 cg. (5 grains) in 300 c.c. (10 ounces) water, to which 1.5 c.c. (24 minims) alcohol is added. The total amount of camphor utilized is thus reduced without interfering with its effective physiological action. The solution is prepared by simply shaking powdered camphor in Ringer's artificial serum, the resulting concentration being .0142 per cent. H. Leo (Deut. med. Woch., Mar. 14, 1918).

Camphor administered in watery solution intravenously in **cardiac weakness in infants**, where subcutaneous injection of camphorated oil acted too slowly. Ampules of 40 to 500 c.c. ( $1\frac{1}{4}$  ounces to 1 pint), of Ringer's solution with a camphor content of .0142 per cent. were used. The cases included **bronchopneumonia**, **capillary bronchitis**, **disturbances of nutrition**, **diarrhea**, and **epidemic meningitis**. In 11 cases the injections had to be made into the sagittal sinus. Good effects were seen in 30 cases; in 8 very severe cases no change occurred, while in the rest the result was doubtful. The action on the respiratory center was more marked than after camphorated oil. R. Schelcher (Munch. med. Woch., Mar. 3, 1922).

Intravenous injections of camphorated oil used very often in the writer's clinic, and he has never observed any untoward effects. He gives 1 c.c. (16 minims) twice daily. He recommends its use in **pneumonia**; even in a practically moribund patient he had striking results. Rudolf Schmidt (Berl. klin. Woch., Oct. 10, 1921).

Intravenous camphor injections act in a few seconds. The dose is 1 to 2 grains (0.06 to 0.12 Gm.) in 10 per cent. oily solution. It may be repeated after  $\frac{1}{2}$  hour. The injection should be given very slowly, taking at least 1 to 2 minutes. The oil must be heated to  $37^{\circ}$  C. Small fat embolisms are absorbed within a few days; death can

occur only if large doses are used. A. Tenenbaum (Polska gaz. lek., Feb. 5, 1922).

Pathologic study in 30 cases in which the measure had been used when the patients were moribund. The oil drop-lets usually showed a general distribution throughout the lungs; there were no oil emboli in diseased areas. Single doses of 5 c.c. (80 minims) of oil are not injurious if not injected too often. Larger doses may cause stasis in the pulmonary circulation, reacting on the heart and vascular system. W. Hüper (Med. Klinik, Mar. 19, 1922).

The duration of unconsciousness in **morphine** and in **carbon monoxide poisoning** is shortened by intravenous injection of camphor in oil. In marked **collapse** benefit is likewise obtained. E. Schilling (Deut. med. Woch., Nov. 2, 1923).

Camphor is extensively used in Europe in genitourinary disorders and particularly in **ischuria**, **strangury** due to the use of cantharides, in the **chordee** accompanying **gonorrhea** or **spermatorrhea** due to general **asthenia**, **abnormal sexual excitement**, and in **cystitis** of bacterial origin when the urine is of acid reaction.

The drug having been employed abroad as a urinary antiseptic, Tyrode requested a specialist in genitourinary diseases to test its efficacy. He obtained good results in a number of cases of **cystitis** with an acid urine, but no amelioration in those in which this excretion was alkaline.

Camphor has long been used in various forms of **diarrhea**, especially those forms termed **choleraic**, **summer**, or **tropical diarrhea**, and **cholera morbus** in which prostration and coldness of the surface occur. It is also recommended in **dyspepsia** and **gastrodynia**, but in small doses, and as a carminative in the **flatulent colic** of infants.

It has been considerably employed in nervous disorders, especially in

**hysteria** and in **insanity** due to **asthenia**, particularly in **melancholia**. It is contraindicated, however, in all conditions with cerebral excitement. **Dysmenorrhea** and the **after-pains** of **parturition** are benefited.

The glandular secretions are somewhat influenced by camphor. While it enhances the activity of the sweat-glands under normal conditions and is thus useful in **colds**, **coryza**, etc., it tends to check the **night-sweats** of **tuberculosis**, because these are due to relaxation of the spiral muscles of the sudorific tubules, which camphor stimulates. The most satisfactory results are obtained by giving it in oil, as in the treatment of pneumonia. Its bactericidal action is thus brought into play. It tends also to check or prevent **hemoptysis** when used in **pulmonary tuberculosis**.

Another useful indication for camphor is in **lactation** when it is necessary, as in **obligatory weaning**, to arrest the secretion of milk. It has also seemed useful in the treatment of **salivation** from any cause.

The best results from internal use of camphor are obtained in **heart weakness** appearing in the course of infectious diseases, such as **influenza**. In **spastic stenosis** of the pylorus the writers claim to have seen notable improvement following protracted administration of camphor; likewise, in several instances, in **spastic occlusion** of the **bile-ducts**. In **exophthalmic goiter**, striking improvement in the thyrotoxic manifestations follows internal use of camphor in conjunction with minute doses of iodine. The tachycardia and restlessness are allayed by additional use of parenteral non-specific protein therapy. Pototsky is quoted as having favorably influenced **nocturnal enuresis** by oral use of camphor. Where camphor is used to reduce spasm of smooth mus-

cle fibers its effect is increased by added use of papaverine. When the optimal results from continued ingestion of camphor have been obtained, the dose should be markedly diminished, to obviate possible cumulative effects. E. Ahlswede and W. Busch (Clin. Med., July, 1924).

*Camphoric Acid*.—This compound has been used mainly in the treatment of **night-sweats** in **pulmonary tuberculosis**. To obtain its best effects, it is said, 15 to 30 grains (1 to 2 Gm.), according to the strength of the patient, should be given dry on the tongue and washed down with a glass of milk or water two or three hours before the sweating usually occurs. Experimental work on camphoric acid has given negative results, and some deny it any anhydrotic action clinically.

The other indications of camphoric acid are similar to those of camphor, but it has been found more efficient in the treatment of catarrhal disorders of the respiratory tract, **acute coryza**, **pharyngitis**, and the **pharyngotracheitis** which often follows winter colds. A  $\frac{1}{2}$  to 2 per cent. solution, used with the atomizer while inhaling vigorously, at times seems very efficient. The drug has been vaunted as a preventive of **catheter fever** following intravesical and intraurethral operations. Fifteen grains (1 Gm.) are given 3 times daily for several days before the operation.

*Monobromated Camphor*.—This compound has been deemed superior to camphor in the treatment of **infantile diarrhea**, especially in the threatening form, **cholera infantum**, the drug having appeared more efficient than many other remedies in the stage of collapse.

In neuroses it seems of value, particu-

larly in **epilepsy**, **hysteria**, **nymphomania**, and **chorea**, in which the cerebrospinal centers are hypersensitive. Being possessed of hypnotic properties, monobromated camphor has been regarded as of special service in these cases when **insomnia** occurs as a complicating factor.

*Camphorated Tincture of Opium.*—

The many uses to which this preparation is devoted depending mainly upon the opium it contains, its therapeutic applications will be studied under **OPIMUM**. Its specific action in **cholera morbus**, which it sometimes arrests in a few moments, warrants, however, specific mention in the present connection.

**Local Uses.**—Camphor and its preparations, the camphor liniment, the soap liniment, and spirit, are used extensively externally for **bruises**, **sprains**, and **myalgia**. In the two latter the liniment, rubbed into the tissues by gentle massage, relieves pain and promotes resolution.

In cutaneous diseases camphor is especially valuable for the relief of **pruritus**. In **pruritus ani**, for example, 1 dram (4 Gm.) of powdered camphor to 1 ounce (30 Gm.) of vaselin, the ointment being applied about and within the anus, is very beneficial. The pain, tension, and burning of vesicular, exudative, and pruriginous affections, such as **eczema**, **pemphigus**, **erysipelas**, and **intertrigo**, are relieved, according to Phillips, by a powder composed of camphor, 40 grains (2.6 Gm.), and oxide of zinc and powdered starch, of each, 1 ounce (30 Gm.). **Furuncles** may be aborted if spirit of camphor is applied early on cotton. **Ulceration** following **carbuncle** may also be checked and caused to heal.

The writer always uses for **wounds**, **bruises**, **sprains**, etc., alcohol, or spirit of camphor and water, in preference to any other applications. On open wounds one or the other is preferable in every particular to bichloride of mercury or any other antiseptic solution. Case of **ulceration** of large dimensions on the nape of the neck, following a very severe case of **carbuncle**, in which pure alcohol (95 per cent.) first, and subsequently spirit of camphor and water, worked wonders. Without their use skin grafting would have been required and perhaps not been successful. B. Robinson (N. Y. Med. Jour., April 6, 1912).

*Camphor-chloral* is mainly used nowadays, applied topically, for the relief of **neuralgia**, while *camphor-phenol* has been found very useful to assuage **toothache** due to an exposed and inflamed pulp, and also as an effective agent for the local treatment of **ulcerations**, especially those of the mouth, *vis.*, in the various forms of **stomatitis** and **glossitis**.

The real field for continued oral use of camphor is **circulatory insufficiency of bacteriotoxic origin**. The drug should be given alone, two to three hours after other agents. Following its use, cyanosis passes off, sensory manifestations are relieved, the breathing is deeper, and the pulse improves. In slow pulse due to digitalis, a favorable effect was noticed; the drug was also used in **angina pectoris**. The writer employed camphocol, a combination of camphor and dioxycholic acid, in 0.1 Gm. (1½-grain) doses. E. W. Taschenberg (Deut. med. Wochenschr., Dec. 15, 1921).

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,  
Philadelphia.

**CANADIAN HEMP.** See **AROCYNUM**.

**CANCER.—GENERAL CONSIDERATIONS.**—In no field of medicine is there greater need for a careful collection of statistics, for painstaking research, and for a judicious correlation of associated facts than in that of cancer. Though the death rate is not so high as in other diseases, notably tuberculosis, it is sufficiently great to afford it few rivals, and, when other features of the disease are considered, one may well doubt whether it is not entitled to the first place among the most dreaded maladies which afflict mankind. Indeed, in New York City during 1922, according to Bulkley, the cancer deaths actually exceeded those from tuberculosis by 934, which was over twice the excess of the preceding year. In cancer there is practically no appreciable tendency toward spontaneous recovery, and but little can be done to check its progress when far advanced, although the disease can be often cured in its earlier stages by proper and adequate treatment, to be mentioned later. Unfortunately, owing to prejudice and the deficiency in the education of the general medical profession, it happens that the removal of cancer in its incipient stages is accomplished in only a small proportion of cases, and too often operation is reached only when it is already too late absolutely to eradicate the disease.

**Frequency of Cancer.**—The actual frequency of cancer and its ethnological distribution are matters of considerable importance. It is difficult, however, to draw correct conclusions on this subject, owing to the unreliable manner in which many of the vital statistics are obtained. This is true even among many of the European

countries. One fact, however, has been definitely demonstrated by statistics, namely, that a higher mortality from cancer coincides with a greater accuracy in the compilation of the causes of death; undoubtedly, this fact explains in a large measure the prevalent belief that cancer occurs with the greatest rarity among the uncivilized races.

In the United States it is estimated that 5 per cent. of all deaths after the age of 30 are from cancer, and it may be conservatively said that about 90 per cent. of its victims die therefrom.

In England it has been estimated that of those living to 35 years of age or over, 1 man out of every 11, and 1 woman out of every 8, dies of cancer. The crude death rate from cancer in England is 0.092 per cent. of the living population; in Wales and Ireland it is 0.079 per cent. Much greater accuracy in regard to the recording of vital statistics is obtained in England than in Ireland or Wales.

In Switzerland still greater accuracy prevails; medical inspection of the dead is customary, and autopsies are performed in 25.7 per cent. of deaths. There the crude death rate from cancer is 0.129 per cent.

In Switzerland there occur about 5000 deaths from cancer a year, corresponding to 12.8 per 10,000 inhabitants or 40.9 per 10,000 people over 40 years of age. There is thus 1 cancer death a year among 780 inhabitants, or among 220 that are over 40 years of age. The two sexes are about equally affected. The seeming increase since 1901 is chiefly due to the better diagnosis of internal cancers. Renaud (*Schweiz. med. Woch.*, Feb. 13, 1926).

In Holland great care is also exercised in the recording of vital statistics, and coinciding with this we find a correspondingly high rate attributed

to cancer, namely, 0.101 per cent. The Prussian statistics are acknowledged to be not very accurate, and the death rate from cancer there is 0.070 per cent.

These figures contrast strongly with those from Spain and Hungary, for which the percentages are, respectively, 0.044 and 0.04 per cent., and still more strongly with the percentage of 0.011 per cent. for Serbia. In some countries the death records are intrusted to laymen and even laywomen, and in Catholic countries the duty is very apt to fall on the parish or district priest. To illustrate how inaccurate the returns may sometimes be: Prinzing cites that in one case an ignorant peasant returned all deaths as due to cardiac failure, and another in Tilsit attributed 50 per cent. of the deaths to diphtheria.

Apparently the death rate from cancer is less in the South and greater in the larger cities than in the country, but this difference may only be apparent on account of the inaccuracy in collecting statistics.

In Lapland cancer is rare; very few cases have been reported. In Africa, Egypt, and Tunis it is also rare. In Australia the death rate from cancer is fairly high. In Tasmania it is 5; in New Zealand, 1907, 9.3; in Victoria States, 6.09 per 10,000 of the living population.

The question of a yearly increase in cancer is an important one, and one upon which there has been considerable difference of opinion. Those authors who have based their conclusions upon the vital statistics state that the death rate from cancer is increasing from year to year.

The death rate from cancer is stated to have increased over the world by 23 per cent. since 1900, and in New York

City, by 30 per cent. Maxwell Williamson, of Edinburgh, has published figures showing that in that city the cancer death rate has steadily risen in the period 1898 to 1920 from 0.88 to 1.39 per 1000 of living persons. That efforts to reduce the death rate may bear fruit even with our present limited knowledge is shown, however, by Hoffman's statement that in localities where the preventive campaign of the Society for the Control of Cancer has been most effective, the rate has unquestionably declined, on account of earlier diagnosis and operative treatment.

Coley collected a large number of statistics from which he concluded that there had been a steady increase in the death rate from cancer. According to the Widows' Life Insurance Company the following table represents the proportion of deaths due to cancer to the total mortality:—

For 29 years from 1815 to 1844, 0.93			
13	"	"	1845 1858, 1.79
7	"	"	1859 1866, 3.00
6	"	"	1867 1873, 4.56
6	"	"	1874 1880, 4.93
6	"	"	1881 1887, 5.44
6	"	"	1888 1894, 6.88

According to Hoffman (Cancer, I, No. 1, 1923) cancer, subsequent to 1913, and in the larger American cities, as indicated by the number of people perishing of this malady out of 100,000, increased from 89 to 91.1 during 1917, and to 124.6 during 1922. From 1912 to 1916 seven cities exceeded the cancer death rate of 100 per 100,000. In the period 1917 to 1921, 38 cities exceeded the cancer death rate of 100 per 100,000.

Each year, in the United States, 100,000 people die of cancer, 85 per cent. of these being over 40 years old. Though it is absolutely certain that

many cases of cancer are either arrested or cured because of early diagnosis and prompt and efficient treatment, this salvage is not shown in statistics.

Of the cities with the highest mortality rate, according to Hoffman, Albany, N. Y., takes the lead with 162.9; thereafter come San Francisco, 161.8; Boston, 145.8; Sacramento, 141.7; Topeka, 137.4; Providence, 135.5, and Los Angeles, 132.0. Norfolk, Va., has a rate of 48.4; Scranton, Pa., 65.0; and Detroit, 60.8.

While the death rate per thousand at Basel in the last 50 years has declined from 23.25 to 12, the cancer rate has increased from 0.86 to 1.31. The ratio of deaths from cancer to the total mortality has thus increased from 3.69 to 10.90 per cent. Jessen (*Schweizer. med. Woch.*, Nov. 18, 1920).

In Switzerland the rate rose from 114 in 1889 to 132 per 100,000 in 1898. In Paris the death rate from cancer per each 100,000 of the population in 1865 was 84. In 1870 it was 91; in 1880, 95; in 1890, 108; in 1900, 106.

In Australia in 1851 the death rate was 14; in 1861 it was 19; in 1871, 25; in 1881, 32; in 1891, 45, and in 1901 it was 57 per 100,000 of the population.

In the United States the general increase in the death rate from cancer per 100,000 inhabitants between the years 1890 to 1900 was 12.1.

Lex, of Heidelberg, found that during the years 1870 to 1879, 6.75 of the autopsies proved to be cancer, and between the years 1900 and 1907, 9.13. Rieck, of Munich, between the years 1854 and 1863, found that 7 per cent. of the autopsies were cancer cases, and between the years 1894 and 1903, 12.5 per cent.

Steinhaus, of Brussels, found that between the years 1888 and 1897, 8.6 per cent. of the autopsies were cancer cases, and between 1898 and 1907, 9.07 per cent.

Nobling published the following table, comprising 1371 autopsies between the years 1903 and 1909. He noticed only a slight increase in cancer cases:—

Year.	Deaths.	Carcinoma.	Per cent.
1903	394	51	12.9
1904	396	54	13.6
1905	441	62	14.1
1906	432	76	17.5
1907	493	100	20.0
1908	643	111	17.3
1909	728	101	14.0

These statistics, taken from the autopsy table, cause some doubt to exist as to how real the alleged increase of cancer is. Many authorities believe that whatever increase there is is limited to an increase of cancer of certain organs, while there is no increase in other organs. Bashford has shown for England that cancer of the uterus is diminishing rather than increasing, while cancer of the gastrointestinal tract has increased slightly. He states that for males the main increase falls on the alimentary tract, especially the stomach. The liver and gall-bladder show no increase. For females the increase, although it also falls mainly upon the alimentary tract, affects likewise the breast, while the uterus, ovary, liver, and skin show no increase.

According to Fichera (*Prensa méd. Argent.*, Aug. 10, 1925), of the  $\frac{1}{2}$  million human beings who die of cancer every year, Europe alone accounts for 300,000, and North America for 95,000. England's deaths number 45,000; France, 24,000; Italy, 27,000, and Argentina, 5696. No climate or race is exempt, but women develop cancer earlier than men, and the disease attacks preferably organs in which there is exceptional cellular activity during their functioning. The alleged increased prevalence of cancer is probably more apparent than real.

**ETIOLOGY.**—It has been the custom until recently to say concern-

ing the origin of tumors, especially of carcinoma, that we know nothing. Man has become so accustomed to this that a nihilistic attitude of mind has resulted. This attitude of mind is not proper, because we are gradually learning more about the etiology, that is, the cause of cancer. A theory which is good only for the origin of *malignant* tumors cannot be held sound, because there is no special dividing line between benign and malignant tumors. There is but a single law for all sorts of tumors.

Schwalbe stated that a satisfactory theory of tumor formation must declare how and why a tumor is developed. The three most promising theories are:

1. Irritation theory.
2. Coal-tar theory.
3. Parasitic theory.

*Irritation Theory.*—The founder of this theory, Virchow, based his conclusions upon the fact that tumors are very frequently in places where chronic irritation, long continued, occurs and where there is a long-drawn-out chronic inflammation. The fact that tumors occur on the site of chronic inflammation, or as a result of it, is found in carcinoma of the gall-bladder and of the kidney.

*Coal-tar Theory.*—An impetus to the study of cancer was given when a study of the shale workers in England disclosed certain facts: (1) that a considerable number of these workers developed epitheliomata of the hands; (2) that the epitheliomata developed even years after the worker had ceased to handle shale; (3) that metastases and deaths occurred. These factors were very ably discussed by different members of the Imperial Research Bureau. Their studies were the incentive for

others as well as themselves to attempt to produce cancer artificially by irritation with coal-tar.

*Parasitic Theory.*—Fibiger, in 1912, through his studies of cancer of the stomach in rats, due to Spiroptera, stimulated studies on the parasitic origin of cancer. The *Bacterium tumefaciens* produces in plants a tumor similar to a malignant tumor in man. After it is fully developed, however, it breaks down and, being invaded by saprophytic bacteria and fungi, becomes an open septic wound.

The etiology of cancer also includes the consideration of a number of factors, all of which have a bearing upon our ideas as to its causation. These will be considered seriatim under the following heads:—

1. The occurrence of cancer in the animal and plant kingdoms.
2. Its distribution according to race and country.
3. Whether or not there is any predilection for certain localities in the same country or city.
4. Its relation to sex and age.
5. The frequency with which the various organs and tissues are affected.
6. The influence of heredity in its incidence.
7. The influence of occupation and diet upon its development.

**Cancer in Animals.**—The close similarity of animal cancer to human cancer has been demonstrated, and certain important facts have been developed, as a result of the cultural propagation of its cells by a process of continued transplantation.

Experiments showing that all diets which gave in normal animals an approximately normal growth curve grew large tumors with a high percentage of takes; all diets which depressed the growth curve retarded or prevented



tumor growth. A study of blood of rats on these diets showed no change in numerical count of red and white cells, but a decrease in number of *lymphocytes* in all diets stimulating cancer growths, and an increase in all diets which retarded tumor growth. From the work it would appear that cholesterol is a factor which, while of little or no nutritive value, favors tumor growth when conditions favorable to its initiation are present. E. P. Corson-White (Trans. Penna. State Med. Soc.; N. Y. Med. Jour., Mar. 1, 1919).

A squamous cell carcinoma has been found in the *Gasterostens spinachia*, and an osteosarcoma has been observed in the operculum of a cod. Carcinoma in the thyroid of the trout is of comparatively frequent occurrence; since the first authentic case was discovered by Gilruth, over 2000 additional ones have been reported. Smallwood, of Syracuse University, has described a carcinoma of the kidney of a frog, and there have been reported 2 cases of carcinoma of the skin in the frog. A carcinoma of the glands of the skin of the *Triton cristatus* has also been reported.

According to Plehn, there are few real tumors in reptiles or amphibians. In fishes the number of growths of various kinds is very great.

Peyton Rous has described a spindle-cell sarcoma growing in Plymouth Rock chickens, and has been able to develop such a degree of malignancy in this tumor that it can be transplanted successfully in 85 per cent. of the pure-bred Plymouth Rocks. A feature of very great significance in connection with these tumors is that they are capable of being *transmitted by a cell-free filtrate*.

In experiments designed to bring out the essential characteristics of a malignant cell, the writer inoculated cultures

of normal large mononuclear leukocytes with a filtered extract of the Rous sarcoma, and found that after about 20 days' incubation these cells, upon inoculation into fowls, caused a rapidly growing tumor which ultimately killed the animal by metastases. Observation of such infected mononuclear leukocytes *in vitro* showed that, instead of continuing to live like normal mononuclears, they usually developed vacuoles and granulations after 3 or 4 days, exhibited less of migration and multiplication, and then progressively disappeared by a process of digestion, though inoculation of the clear supernatant fluid into fowls nevertheless induced highly malignant tumors in a short time. Thus, the penetration into large mononuclears of the agent of Rous sarcoma gave those cells the property of secreting the Rous agent and of dying prematurely. Yet such cells are far from being anarchic, or from possessing as much growth energy as an embryonic cell, as is supposed according to the classical hypotheses.

That such cells of low resistance and short life can build up a tumor having the power of unlimited growth in the body is accounted for as follows: When the Rous agent enters a fowl, it is soon destroyed by the humors unless it is taken up by a tissue macrophage or a monocyte. The infected macrophage continues to multiply and infect other macrophages, though it eventually dies. Then the dead macrophages attract normal macrophages, which become modified in their turn. Meanwhile, the growth-promoting substances in the macrophages are set free, and bring to the fibroblasts and other cells of neighboring tissues the food material and stimulus necessary for multiplication. Since the Rous agent propagates itself within the cells, this process can go on indefinitely. Thus, herein, the macrophages are no longer defenders against bacteria and foreign substances, but actually protect the Rous agent against destruction by the humors. A. Carrel (Jour. Amer. Med. Assoc., Jan. 17, 1925).

Among mammals, malignant tumors are found with rather surprising frequency; as might be expected, they occur most often among those animals with which we are most familiar, the horse, dog, mouse, and rat. One cannot but believe that systematic search would reveal a yet more widespread distribution of cancer throughout the animal kingdom.

The identity of these animal tumors with human cancer has often been questioned.

Von Hanseemann denied that these animal growths correspond to human cancer, but we cannot agree with his reasons. Whether these new growths, particularly those growing in rats and mice, represent the same pathological condition as true human cancer is a matter of considerable importance, affecting not only many facts of prime importance in tumor growth, but also our ideas of immunity in cancer and of the susceptibility of malignant new growths to a more ideal method of treatment than at present exists.

Apolant (Berl. klin. Woch., 1912, xlix, 495) undertook, very successfully it seems, to answer von Hanseemann's arguments.

In almost every respect, though there are quantitative differences, the features of animal cancer answer to our criteria for the disease as it occurs in the human race. This includes their histological structure, their invading characteristics, their clinical course, and finally their ability to form metastases. The latter is, perhaps, the most important of all.

Hanau, as early as 1889, described metastases in the lymph-nodes of a rat with a primary epithelioma; this tumor he successfully transplanted. Borrel, in 1903, recorded pulmonary

metastases in a large proportion of the mice spontaneously developing cancer. Borrel and Haaland described later an epithelioma developing in the paw of a mouse, and showed that the *metastases originated in minute emboli*, which became lodged in the branches of the pulmonary artery and *then grew backward*. Leon Michaelis, who described a carcinoma in a rat, recorded metastases in the transplanted tumors. In the transplanted sarcoma of the rat described by Flexner and Jobling, metastases also occurred. Among the tumors resulting by inoculation from 70 spontaneous primary tumors which furnished working material for the laboratory of the Imperial Cancer Research Fund, 50 per cent. produced metastatic growths.

In the clinical course of these tumors there is a striking similarity to human malignant growths. This is noted in the character of the tumor elements, in their rapidity of growth, and in their invading characteristics. It is also shown by the large size which they attain, the frequent recurrence after operation, and the rapidity with which recurrence is likely to follow after the first operation, as compared to the rather long period of quiescence succeeding a second operation.

*Utilization of Animal Cancer in the Study of Human Cancer.*—The employment of these tumors in various modes of experimentation has furnished a new series of facts which are applicable to the problems of human cancer. Among the most interesting of these are the conditions under which these tumors can be transplanted into other animals. These conditions concern the age and the adaptability of the inoculated animals, the quantity and degree of comminution of the material used for in-

oculation, and, what is most important, the particular period of growth in which the tumor may be at the time of inoculation. Regarding the *age* of the inoculated animals, in general, younger mice are more susceptible to successful implantation than older ones; but there is also noticed, aside from youth, a tendency for the tumor tissue to adapt itself more readily to animals of approximately the same age as those from which the tissue for transplantation is taken.

Murray and Woglom (Seventh Scientific Report of the Imperial Cancer Research Fund, p. 45, 1921) believe that the period of life cycle of the mice in which cancer developed from the painting of tar on the back corresponded to about the 35th year in man.

Tumors are much more readily transplanted into native mice than into mice from other countries. On the other hand, after a tumor has been growing for a longer or shorter time in a mouse of a foreign country, it loses its ability to again grow so well in a mouse from the same country as that to which the original host of the tumor belonged. *Adaptability*, therefore, is a very important characteristic of cancer cells.

The subdivision or *comminution* of the material used for transplantation greatly affects the chances of successful inoculation. The method adopted by the laboratory of the Imperial Cancer Research Fund is more successful than other methods utilized. In this laboratory the cancer material is divided by a specially constructed hashing machine devised by Haaland, and certain definite amounts of the tissue thus cut are injected subcutaneously, without dilution. This method is more successful than when larger pieces are implanted, or when the cancerous tissue

is ground up in a mortar, and it also permits of more accurate dosage.

A particular form of tumor in mice (hemorrhagic tumors), which Ehrlich succeeded in transplanting successfully only once in 500 times, Gierke, of the London laboratory, was able to inoculate easily; in one series he obtained even 100 per cent. of successes. Of the total number of spontaneous tumors, Ehrlich succeeded in transplanting only 14 per cent., whereas 80 per cent. have been propagated by the workers in Bashford's laboratory. Animal tumors, at least in the form of carcinoma in mice, show great fluctuations in the percentages of successful inoculations during consecutive transplantations. The *fluctuations occur periodically in wave-like curves*, and corresponding with them are *similar fluctuations in the rapidity of growth of the tumor*.

*Transmutation of Morphological Type.*—Such fluctuations in malignancy strongly suggest accompanying biological alterations of the tumor-cells during successive transplantations; extensive changes of this kind have been shown to occur by Murray in certain epithelial cancers of mice. These cancers will so change their morphology that at one time they conform to an adenomatous type, and at another time present the appearance of epithelial tumors, associated with excessive keratinization, and yet again acquire adenomatous characteristics.

The most interesting change of all which *carcinoma* in mice undergoes is a transition *into sarcoma*. This, however, cannot be spoken of as a metaplasia of the epithelial cells; it is rather a *replacement* of one form of tumor by another, which spontaneously develops from the transplanted stroma. This has been proved by microscopic

examinations made at intervals of eighteen to forty-eight hours after transplantation. In the process of transition of carcinoma into sarcoma there is first formed a mixed tumor; and in the development of such a growth the cells of the transplanted connective-tissue stroma no longer degenerate, but begin to proliferate and show numerous mitoses, even within twenty-four hours after transplantation.

*Inoculation of Tumors into Animals of Different Species.*—Many attempts have been made to transplant these tumors into human beings, and, with three or four claimed exceptions, these attempts have universally failed. Of 400 attempts made by Sticker (Zeitschr. f. Krebsforsch., 1908-09, vii, 55) to inoculate human cancer into mice and rats no case was successful. Metchnikoff never succeeded in inoculating human cancer into apes. It is also impossible to inoculate the animal tumors into animals of different species.

Salivary tumors from a Japanese mouse cannot be transplanted into a white mouse. Jensen transplanted a tumor of a white mouse into a house mouse, but did not succeed in transplanting it into a field mouse.

In a series of 12,000 necropsies on the bodies of mice there were found 87 mice with neoplasms meeting all the criteria of sarcoma. Metastasis was observed in 23 cases, or 26.4 per cent., the osteoid sarcomas leading with 75 per cent. Metastasis occurred in only 13 per cent. of the spindle-cell sarcomas. Lungs, liver and lymph nodes showed most of the metastases. In all respects these sarcomas of mice correspond with the sarcomas of men, although the authors found no examples of melanosarcoma, multiple myelomas, or myeloid sarcoma. As with human tumors, mouse sarcomas frequently arise at the site of a trauma, and this has been observed in 11 of the

writer's series. It is evident to them that they have no knowledge of how many of the other mice had received injuries at the point at which they subsequently developed a sarcoma, for the life of a mouse is beset with many accidents and deeds of violence. Especially among the males, wounds are often received in fighting. Slye, Holmes and Wells (Jour. of Cancer Research, Jan., 1917).

J. A. Murray (Imperial Cancer Research Fund, 75-84, 1923) found that the presence of *tar cancer* in a mouse seems to inhibit the secondary production of tar cancer. In mice the induction of a fresh primary growth after a first has been definitely established meets with a very intense resistance. Whether the first tumor is of the same parent tissue or another, the nature of this secondary refractoriness to growth is obscure. It is not a resistance to growth, as shown by the occurrences of metastases and the success of autoplasty. It is apparently an inability to react with cancerous proliferation to procedures which initiate it with certainty in normal animals. Nor has it anything in common with the well-known acquired resistance to the growth of transmissible tumors.

Fibiger has produced experimental tar cancer in such resistance animals, and the development of spontaneous mammary carcinoma has likewise been recorded in these so-called "immunes."

As confirmation is to be noted the rarity of multiple malignant growth in the same individual. Murray states that the above give "an indication of a systemic constitutional change in the organism in which cancer has developed: A change which, if it could be recognized with certainty and rapidity, would enable

us to recognize cancer in its earliest stages, and could we produce it without initiating new growths, would place in our hands a rational means of prevention."

If a filtrate of chicken sarcoma is injected into the pectoralis muscle of a chicken, a positive result occurs more easily when to the filtrate a small quantity of kieselguhr (an infusorial earth) is injected. The writer also believes that the secondary growth of the sarcoma through the injection of a virus is helped by the alterations in the tissues which are produced by the proliferation of cells at the point of injury, because it is found that growth occurs at this point. When the injured tissue is transplanted to other chickens, in a number of cases it has been proved that a tumor is produced. Sound tissue from the same organ in an uninjured area has never caused a tumor to develop. Tissues from other organs never caused formation of a tumor. The author removed the kidney of an animal in which the virus had been injected; upon injection of the kidney tissue into an animal, a tumor was produced. This tumor growth, however, was probably the result of some of the virus being with the blood in the kidney. Young connective tissue is influenced more readily by the virus, and the period of greatest influence lies between the 2d and 4th days after the injury; after older injuries activity of the virus at the injured place occurs less frequently. Virus which is injected through the circulation disappears very quickly. F. Pentimalli (Zeit. f. Krebsforschung, Dec. 15, 1924).

*Influence of the Pituitary Body in the Incidence of Tar Carcinoma in Rabbits.*—L. Sell (Zeit. f. Krebsf., i, 1, 1924) found that in animals the injection of pituitary seemed to hinder the development of irritation cancer from tar, i.e., that the period of time in which it was necessary to apply tar to the animal before cancer developed was increased.

In these experiments each animal was

painted at first twice a week, later once a week, on the entire outer surface of the right ear. (The tar was that which remained after distillation over 350° C.) Alternate animals received weekly an injection of ½ ampule of pituitary, Roche (10 per cent. extract of posterior lobe). None of the animals showed any toxic reaction. No metastases were observed. The more compact the tumor, the earlier the cancer. There always was hornification, and in the deeper parts, epithelial perles were present. In all of the 20 animals painted with tar, tumors developed on the painted area. Some also developed tumors on areas which had not been painted. This was probably the result of rubbing of the tar over these areas. Whether this indicates a tendency for tar to produce tumors in a place distant from the area of the tar application is difficult to determine. (Lipschutz claims that the tar produces a toxic state of the animal which induces the formation of tumors even at a distance from the place of local application.)

Among 9 injected animals, there was 55.5 per cent. of cancer production. The average time was 94 days. The hyperplasia average time was 84 days. These animals became thinner than those not given pituitary. Possibly the latter hindered the growth somewhat, perhaps through contraction of the vessels, thus producing a continuous reduction of skin metabolism with slower production of new cells.

Out of 11 animals not injected with pituitary, 91 per cent. developed cancer. The average time was 77 days. The hyperplasia time averaged 50 days.

There is a close relationship between the hypophysis and the skin and the hypophysis and cell productivity. Tar possibly has a general action on the animals, as is indicated by the production of white hairs in black areas of the skin. This points to a disturbance in the pigment formation which indicates a generalized action of the tar in the rabbit's economy.

L. Seel noticed in experiments on rabbits that in spite of a well marked epithelioma of the skin the animals were not sick, but had good appetites, fur, and libido. He believes that the tar causes the signs and symptoms of cachexia, and finds that when the tar applications cease, the animal again

appears healthy. Also, the cancer is a secondary symptom of tar disease. It is possible, as witnessed in 2 cases of rabbit tumors, for cancer to change into non-malignant growths. More than one cancer can occur at one time.

**Geographical Distribution.**—In the discussion of the frequency of cancer we have already seen that the accuracy with which statistics have been collected materially affects our ideas of the relative frequency of cancer not only in different countries, but also in different races in the same country.

Another factor which accounts for the greater frequency of cancer in England, Germany, and the United States in later years as compared with very much earlier periods is the steadily increasing average length of life. Cancer is a disease which belongs peculiarly to the later years of life, and, for this reason, more individuals are permitted to develop cancer because there are more living at the cancer age than there were some years ago. All the above considerations explain in a good measure the prevalent idea that cancer is infrequent in Japan, China, India, and very rare among uncivilized races. According to statistics, however, cancer would appear to be more frequent in Japan than in Spain, Serbia, or Hungary, and only one-half as frequent as in England. If allowance be made for variation in the reliability of the records of these countries, it is probably as frequent as in England.

The statistics for Japan were collected by Baelz, at the suggestion of the workers of the Imperial Cancer Research Fund, and are all the more remarkable when considered in connection with the remark of Baelz at the time the investigation was re-

quested. He stated at that time "without doubt cancer is much rarer in Japan than in Europe, and the correctness of this opinion is demonstrated by the relatively large number of cases which occur among the small number of European inhabitants in Japan, as contrasted with the rarity with which the disease is observed among the natives themselves."

In India, out of a population of 300,000,000, with all the inaccuracies that exist in the collection of vital statistics (and recognizing the comparatively small proportion of the population, especially among women, who seek treatment at the European hospitals in that country), over 2000 cases of cancer were reported during the three years preceding 1908. Keatinage reported 297 cases treated in the government hospitals during that time.

Cancer has been found among the natives of tropical Africa, and in the various Fiji Islands. In judging, however, of the relative infrequency of cancer in uncivilized countries one must take into consideration the shorter duration of life in these regions. Thus, Pitchford states, on behalf of the Natal Cancer Research Committee, that only 13.7 per cent. of the natives in Natal reach the age of 40 years, while in England and Wales 25.7 per cent. of the population are 40 years old or over.

Most authorities believe that cancer occurs more frequently in the higher classes of society than in the lower. In fact, statistics from civilized nations and from the higher walks of life show that such is the case. Possibly such statistics are more accurate for the higher classes of society and the difference indicated only apparent.

In this country cancer appears to be much more infrequent among negroes and Indians than among the white population. In Virginia, South Carolina, North Carolina, and also Georgia, the following table arranged by I. Levin illustrates the ratio:—

Virginia:				
White	1,190,000	397	1 in	3,000
Negro	660,000	136	1 "	5,000
South Carolina:				
White	560,000	147	1 "	4,000
Negro	780,000	144	1 "	5,500
North Carolina:				
White	1,250,000	326	1 "	4,000
Negro	630,000	84	1 "	7,500
Georgia:				
White	1,200,000	290	1 "	4,000
Negro	1,000,000	161	1 "	6,000

McConnell has given the following table, comprising 17,286 cases and showing the location of cancer in the two races:—

Organ.	White.		Colored.	
	Male.	Female.	Male.	Female.
Abdomen ....	463	631	8	5
Bladder .....	125	49	4	2
Brain .....	12	14	1	
Breast .....	36	1256	2	50
Extremities ..	33	25	3	1
Eye .....	12	6		
Genitals .....	48	51	1	1
Head, face, neck .....	521	255	10	5
Kidney .....	40	47	1	2
Larynx .....	55	11		
Liver .....	720	1024	22	18
Lung .....	30	40	1	2
Mouth, tongue, neck .....	477	133	10	6
Ovaries .....		76	...	4
Penis .....	20			
Rectum .....	271	279	9	15
Stomach .....	2140	1964	55	61
Testicles .....	7	...	1	
Uterus .....	...	2164	...	127
Undetermined	1223	2500	27	84

Levin (*Zeitschr. f. Krebsforschung*, ix, 422, 1910) has shown the great rarity of cancer among the American Indians. Among the population of 155,455 Indians there were collected only 29 cases of cancer, which occurred between the ages of 35 and 59 years.

The rarity of cancer among the Indians cannot be accounted for by the age factor. Statistics show that the average life of the Indian is much longer than that of the white man. Between the ages of 6 and 89 years there were in the United States, per 1000 of the general Indian population, 207.81 Indians, against 219.12 white individuals. Between the ages of 95 and 99 years there were 67.93 Indians, as against 65.28 whites, per 1000 of the total population, and 537 Indians per 1,000,000, as against 51 whites, over 100 years of age.

In contrast to cancer, tuberculosis and diseases of the digestive tract are very frequent among the Indians, while, on the other hand, worry is almost unknown among them.

By actual statistics cancer is very infrequent in Africa and the South Sea Islands, and among the aborigines of Australia. However, the inaccuracy of the statistics, discussed on another page, may account for its rarity in these countries.

Rayburn states that cancer is unknown in Buenos Ayres, yet in the southern portion of the Philippine Islands cases have been reported, *e.g.*, in Bobol and in Sibutu, the latter in the extreme southern island of the Philippines. In 1902, 301 cases of cancer were reported from the whole Philippines. These cases came from every province with the exception of three. All told there were 329,671 deaths during the same year from all causes in the Philippine Islands, but Dudley ("Cancer in the Philippines," *Jour. Amer. Med. Assoc.*, 1, 1908, 1663), from whom these figures are quoted, states that the number of deaths from cancer could be multiplied by 100, and on this assumption he believes that cancer is more frequent in the Philippines than in the United States. The Filipino is a vegetarian by necessity. He lives al-

most exclusively on rice and starchy tubers, varied with a little fish or other sea food. The vast majority never taste meat, and, if, therefore, cancer is more frequent in the Philippines, a vegetarian diet cannot be considered a reason for the apparent immunity of cancer among the southern, uncivilized races.

Little evidence exists that cancer originates with special frequency in certain localities or houses. The supposition, however, that it does has given rise to the term cancer district or cancer house.

A very striking illustration of this character has been furnished by Anton Sticker. He gives information concerning a town whose name he is not permitted to give. He states that in this town there occurred, in the years 1825 to 1865, 10 cases of cancer. All these occurred in two houses in a certain low street where most of the houses had damp cellars. During the next ten years there were 4 cases, 2 of which were on the same street. During the next ten years 7 cancer cases occurred in the same town, 5 of which were on the same street; in the following ten years there were 10 cases, 7 of which were upon this same street, and in the year 1895, 21 cases occurred on this street and only 8 cases in the rest of the town. From 1895 to 1905, 25 cases occurred, 16 of which were on this street.

It cannot now be definitely asserted that cancer is not a transmissible disease. The writer alludes to a group of houses in a small village in which there were 10 deaths from cancer in 14 years, and to Bazin's observation of 8 cases in a group of 7 houses, as well as of 3 instances in which dogs and their masters successively developed cancer. C. Fiessinger (*Bull. de l'Acad. de méd.*, Mar. 4, 1924).

It has also been shown by Hislop that in New Zealand the disease occurs more frequently according to certain climates of rather definitely described regions, but it could not be shown to depend in any way upon diet or manner of life.

It must be quite evident, therefore, that cancer occurs among all races, and also that it shows no predilection for one race, or for any special localities upon the globe. It is true that epidemics have been reported, particularly along certain rivers, but apparently little importance can be attributed to them.

While 659,528 persons died in the Civil War, there were 1,021,513 deaths from cancer alone in the United States between 1900 and 1915. In Porto Rico during 1915 there was one death from cancer every day, and in the city of San Juan last year 3 deaths every month. Aviles (*Bol. de la Asoc. Med. de Puerto Rico*, Mar., 1918).

Cancer has formed from 1.09 to 1.35 per cent. of the total mortality of the island since 1912. In the public hospital there have been 151 cases of cancer since its opening in 1909; the growth was inoperable in almost 50 per cent. The uterus was the seat of the malignant disease in over 33 per cent. Del Toro (*Bol. de la Asoc. Med. de Puerto Rico*, Mar., 1918).

**Distribution in the Body.**—Of considerable importance from the etiological standpoint is the frequency with which cancer attacks the various tissues or organs of the body, that is, its distribution within the body itself, and, inasmuch as this phase of the subject is so intimately connected with the relative frequency of cancer in the two sexes, many of the tables designating both the sex as well as the portion of the body affected, it will be convenient to discuss both these factors together.

In a study of cancer mortality in the 10 original registration states of the United States from 1900 to 1920, the writer found the following death rates per 100,000 of population for various organs (the first figure in each instance representing the deaths per 100,000 in 1900 and the second figure,



in 1920): Buccal cavity, 5.50, 11.18; stomach and liver, 77.1, 116.2; peritoneum, intestine and rectum, 19.0, 47.2; female genital organs (women aged 40 or over), 51.8, 84.0; breast (women aged 40 and over), 34.4, 62.8; skin, 7.36, 9.38; other or unspecified organs, 60.75, 54.9. For cancer, all forms, the deaths per 100,000 were 212.0 in 1900 and 311.4 in 1920. From these figures the percentage increase for each group during this period works out thus: Buccal cavity, 103.4 per cent.; stomach and liver, 50.7 per cent.; peritoneum, intestine and rectum, 148.4 per cent.; female genital organs, 64.7 per cent.; breast, 82.6 per cent.; skin, 27.4 per cent.; other organs or organs not specified, decrease of 9.6 per cent.; cancer, all forms, increase of 46.9 per cent. About 30 per cent. of this general increase in cancer is due to greater precision and accuracy in the filling out of death returns. The remainder, however, is an actual increase in mortality, resulting in a death-rate between 25 and 30 per cent. higher in 1920 than in 1900. It is significant that the death-rates of some of the cancers in accessible sites such as the buccal cavity, breast and uterus showed a higher percentage increase than cancer in an inaccessible site, such as the stomach and liver. The recent change in predominant racial stocks of immigrants from northwestern Europe to southeastern Europe had no part in the cancer increase is indicated in that cancer death rates, according to available statistics, seem lower in the latter than in the former stocks. Nor did the increased cancer death rate appear to be dependent upon changes in age distribution. J. W. Schereschewsky (Jour. Amer. Med. Assoc., Oct. 17, 1925).

Cancer is unquestionably far more frequent among women than among men. This fact is to be attributed to the large number of cancers which occur among women in the uterus and breast. There are no corresponding organs among men similarly attacked. The large number of cancers of

the stomach help to swell the male proportion, but by no means in a manner peculiar to men. Peller found that the more pregnancies a woman had, the later cancer became manifest; he assumes that pregnancy produces a certain amount of protection against carcinoma.

Buday has arranged the following table, which illustrates the greater frequency of cancer among women in all countries:—

	Cases among women.	Cases among men.
United States .1900	171.0	to every 100
Sweden .....1890-98	153.8	" " "
England .....1901-05	147.0	" " "
Italy .....1904	127.8	" " "
Hungary .....1901-04	124.7	" " "
Germany .....1907	123.0	" " "
Austria .....1895-98	121.0	" " "
Switzerland ....1901-06	100.2	" " "

For the United States McConnell gives the following table illustrating the relative frequency of cancer in the various organs of the body in percentages for every 1000 deaths from cancer:—

	F.	M.	Total.
Abdomen.....	76.9	92.4	82.8
Bladder.....	6.2	25.0	12.5
Brain.....	1.7	2.6	2.0
Breast.....	157.8	7.5	
Eye.....	0.7	2.4	1.3
Genitals.....	6.3	9.6	
Head, face, neck.....	31.1	104.2	59.2
Larynx.....	1.3	10.8	4.9
Lower extremities.....	2.1	3.7	2.7
Lungs.....	5.1	6.1	5.5
Mouth, tongue, throat...	16.8	95.5	46.8
Ovaries.....	9.7		
Penis.....		3.9	
Rectum.....	35.5	59.9	42.9
Stomach.....	244.7	430.6	315.6
Testicle.....		1.6	
Upper extremities.....	1.1	3.3	1.9
Uterus.....	276.8		

The following table shows the frequency with which some of the more important organs are attacked in the two sexes, arranged in the order of frequency with which cancer occurs in them. Undoubtedly the majority of the cancers of the liver are secondary growths. Primary cancer of the liver is comparatively infrequent:—

	Male.
Stomach .....	430.6
Liver .....	145.6
Head, face, and neck .....	104.2
Mouth, tongue, and neck ...	95.5
Lower body .....	92.4
Rectum .....	54.9
	Female.
Uterus .....	276.2
Stomach .....	244.7
Breast .....	157.8
Liver .....	125.9
Lower body .....	76.9
Rectum .....	35.5

The following statistics given by Redlich (Zeitschr. f. Krebsforschung, 1907, vii, 261), Feidchenfeld (I. D., Leipzig, 1901), and Riechelmann (I. D., Rostock, 1902) afford a more accurate estimation of the true distribution of cancer within the body, as it is based upon autopsy material. It shows the total number of cancer cases for each organ coming to autopsy within a certain definite time and the percentage which this number is of the whole:—

Organ.	Redlich.		Feidchenfeld.		Riechelmann.	
Stomach .....	176	35.5	165	32.5	288	40.5
Intestines .....	59	11.9	56	11.0	59	8.3
Rectum .....	31	6.3	27	5.3	26	3.65
Large gut .....	25	5.0	23	4.3	26	3.65
Intestinal .....	3	0.6	6	1.2	7	1.0
Esophagus .....	55	11.1	58	11.4	77	10.8
Gall-passage .....	33	6.6	26	5.1	47	6.6
Gall-bladder .....	22	4.4	21	4.1	39	5.5
Gall-ducts .....	7	1.4	4	0.8	8	1.1
Bladder and ducts .....	4	0.8	1	0.2		
Lung .....	31	6.3	22	4.3	27	3.8
Uterus .....	30	6.0	45	8.9	86	12.1
Uterus and vagina .....	7	1.4	7	1.4		
Ovaries .....	11	2.2	12	2.4	14	1.9
Other genital organs .....	4	0.8	11	2.2	5	0.7
Vagina .....	2	0.4	7	1.4		
Vulva and vagina .....	1	0.2	4	0.8		
Parovarium .....	1	0.2				
Breast .....	27	5.4	32	6.3	30	4.2
Pharynx .....	11	2.2	4	0.8	4	0.6
Pancreas .....	9	1.8	13	2.6	19	2.6
Kidney .....	8	1.6	4	0.8	2	0.3
Skin, esp. face .....	7	1.4	4	0.8	8	1.1
Liver .....	5	1.0	7	1.4	3	0.4
Bladder .....	4	0.8	7	1.4	6	0.8
Lip .....	3	0.6	1	0.2		
Thyroid .....	3	0.6	1	0.2	5	0.7
Prostate .....	2	0.4	2	0.4	2	0.3
Nose, pharyngonasal .....	2	0.4				
Penis .....	1	0.2	1	0.2	2	0.3
Lower jaw .....	1	0.2			1	0.15
Tongue .....	1	0.2	6	1.2	7	0.9
Larynx .....	1	0.2	3	0.6	7	0.9
Trachea .....	1	0.2	2	0.2		
Ureter .....	1	0.2				
Questionable .....	3	0.6	3	0.6	2	0.3

The same table arranged according to the frequency among the two sexes is shown below and on following page.

	Male.	Female.	Total.
Redlich .....	283	213	496
Feidchenfeld .....	253	254	507
Riechelmann .....	362	349	711

	Redlich.				Feidchenfeld.				Riechelmann.			
	Male.		Female.		Male.		Female.		Male.		Female.	
Stomach .....	113	39.9	63	29.6	101	39.9	69	25.2	169	46.6	119	34.1
Esophagus .....	49	17.3	6	2.8	54	21.3	4	1.6	72	20.0	5	1.4
Lungs .....	26	9.2	5	2.3	20	7.9	2	0.8	21	5.9	6	1.8
Rectum .....	19	6.7	12	5.6	13	5.1	14	5.5	18	5.1	8	2.3
S. intestine .....	12	4.2	13	6.1	11	4.3	11	4.3	13	3.7	13	3.9
Pharynx .....	11	3.9			3	1.2			2	0.6		
Gall-passage .....	10	3.5	23	10.8	3	1.2	23	9.1	14	3.9	33	9.5
Pancreas .....	7	2.5	2	0.9	7	2.8	6	2.4	11	3.1	8	2.3
Kidney .....	6	2.1	2	0.9			4	1.6	2	0.6		
Skin .....	5	1.7	2	0.9	3	1.2			6	1.7		
Bladder .....	4	1.4			5	2.0	1	0.4	3	0.8	2	0.6
Liver .....	3	1.1	2	0.9	5	2.2	2	0.8	1	0.3	2	0.6
Prostate .....	2	0.7			2	0.8			2	0.6		
Thyroid .....	2	0.7	1	0.47	1	0.4			1	0.3	4	1.2
Hip .....	2	0.7	1	0.47	1	0.4					4	1.2
Nose-space .....	2	0.7										
Duodenum .....	1	0.35	2	0.9	3	1.2	3	1.2	2	0.6	2	0.6
Breast .....	1	0.35	26	12.2	3	1.2	32	12.6	2	0.6	29	8.3
Penis .....	1	0.35			1	0.4			2	0.6		
Vagina and vulva ...	1	0.35	3	0.56			11	4.4			5	1.4
Lower jaw .....	1	0.35							1	0.3		
Tongue .....	1	0.35			5	2.0			4	1.2		
Larynx .....	1	0.35			3	1.2			7	2.0		
Questionable .....	3	1.1			2	0.8			1	0.3	1	0.3

**Influence of Age.**—Cancer shows a very definite predilection for certain ages. The majority of cases of cancer occur between 50 and 60 years of age. The following table gives the average age for the development of cancer in the countries mentioned:—

	Years.
Holland .....	60.5
Denmark .....	59
Sweden .....	57
Germany .....	52.5
United States .....	52.2
France .....	50
Austria .....	48
Japan .....	47
Hungary .....	46.5
Portugal .....	37

Redlich gives the average age for men as 56.4 and women 55.5. He gives the following table for 367 cases:—

	Female.	Male.	Total
10 to 20 .....		1	1
21 " 30 .....	4	6	10
31 " 40 .....	18	18	36
41 " 50 .....	93	59	152
61 " 70 .....	76	43	119
71 " 80 .....	22	26	48
81 " 100 .....	1		1

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Cancer is very rare among children, yet Phillips and Lindermann (Zeitsch. f. Krebsforschung, 1908-09, vii, 682) have given statistics of a considerable number of cases in early childhood. Phillips reported 5 cases of epithelioma of the skin in children from 8 to 12 years of age, aside from numerous other cases of new growths of the lymphatic glands in which it was impossible to distinguish between carcinoma and sarcoma.

Carcinoma of the lung has been reported in a boy 5½ years of age. Epithelioma of the larynx has been reported in a child 10 years of age. There have been reported 22 cases of medullary cancer of bones in children from 8 months to 15 years of age; 5 true cases of carcinoma of the adrenals in children from 11 months to 12 years of age.

Pancreatic sarcoma has been reported in 3 children 6 months, 2 years, and 13 years of age. There have been reported

11 cases of carcinoma of the liver in children between the ages of 1 year and 14 years. No case of cancer of the esophagus has ever been reported in children. Cancer of the stomach has been reported in a child 5 weeks old, in a girl 13 years old, and in a boy 14 years old. Primary cancer of the intestinal canal is the most frequent form of cancer in children. There have been reported 37 cases, of which 26 are certain. The age of these vary between  $1\frac{1}{2}$  to 15 years. The majority have been between 12 and 15 years of age. At least 11 cases of cancer of the rectum have been reported in children between 11 and 15 years of age. Cancer of the kidney is most frequent in early childhood; besides various forms of medullary sarcoma there occur adenocarcinoma, alveolar carcinoma, and hypernephroma. But if the sharpest criticism is applied there is only 1 case in which the diagnosis is positive; this is one of Perthe's cases, in a boy 9 years of age who had a true adenocarcinoma of the kidney. Twenty-one cases of cancer of the ovary in children have been reported; the ages have varied between 11 and 15 years. All told Phillips has reported 390 cases, and states that 87 of these stood a severe diagnostic test. Epithelial cancer occurs but rarely in childhood. Its greatest frequency is at puberty, and the organs most affected are the skin, intestinal tract, and ovaries.

There does not appear to be any essential predilection for cancer occurring in childhood for one sex more than for the other.

**Hereditary Influences.**—Much discussion has been indulged in upon the part played by hereditary influences in the development of cancer.

Cullen has reported cancer of the uterus occurring in three sisters, and believes that hereditary influences play an important part in the etiology of such cases. Paget maintained that cancer occurs more frequently in the antecedents of cancer patients than in others. Among 2389 women with cancer reported by Pierson from the Middlesex Hospital in London, 359 had family histories of cancer, while of the antecedents of 753 non-cancer cases only 120 were affected with cancer. According to this, cancer seems to be no more frequent in the families of patients with cancer than among those without it. Guillot has found a history of cancer in 11 per cent. of antecedents of non-cancerous patients and in 17.4 per cent. of the antecedents of cancer patients, and he estimates that the incidence of cancer in the parents of non-cancer cases is 16 per cent., as against 17 per cent. of the parents of cancer patients.

The famous case of Madame Z, reported by Ledoux-Lebard, furnishes striking support to believers in the influence of hereditary factors in the causation of cancer. There were 15 of the descendants of this woman who had cancer out of 26 offspring—1 of 7 males and 14 of 19 females.

It is a well-known fact that the offspring of certain gray stallions develop melanoma with especial frequency. Xeroderma pigmentosum is prone to occur in members of the same family.

Tyzzier showed that, of the offspring of a certain female mouse with a tumor of the lung, 65 attained the age of 6 months, and, of these 65 mice, 20, or 32 per cent., presented tumors, 17 of the same type as the parent.

Bashford has maintained that among human beings in England there is no conclusive evidence that heredity plays a part in the causation of cancer.

Among men aged over 35, cancer occurs in 1 out of 11. Among women over this age, 1 out of 8 dies of the disease. Therefore, few families escape, and it is difficult to form a correct idea as to hereditary influences. Of 2932 cases reported by Bashford, only 669 were available for statistics from the hereditary standpoint; 358 of the latter were without relatives who had had cancer, while 311 had such relatives. These 311 individuals had 359 relatives who had cancer, and among the 359 relatives there were 58 fathers and 114 mothers; 58 bear a ratio of 1:11.5 to 669, or the total number of cases available for hereditary statistics, and 114 bear the ratio of 1:6. These ratios correspond to the normal frequency of cancer.

In the "Fourth Scientific Report of the Imperial Cancer Research Fund," however, Bashford states:—

"Precise evidence is advanced of the existence of a hereditary predisposition to the development of spontaneous cancer." "While at present it is not possible to explain how the hereditary liability to the development of spontaneous cancer is transmitted, it can be assured with certainty that it does not consist in the inheritance of a soil more suitable for the growth in general." "There is a considerable amount of evidence to show that the *predisposition is not a general one* affecting the entire body equally, but that the *tendency transmitted affects mainly one organ system*, so that groups of animals may ultimately be obtained in which different organ systems will present a definite predisposition."

Levin (Zeitschr. f. Krebsforschung, xi, 547, 1912) attempted to study the influence of heredity on cancer from a somewhat different standpoint, and arrived at the following conclusions: (1) That *resistance to cancer is a dominant character whose absence creates the susceptibility to cancer*; (2) that the *susceptibility is specific in different families for different organs*. He considers that the conclusions to which he came in a previous study, that hereditary disposition has no influence on cancer, may have to be revised. Both

Bashford and Levin, therefore, have changed their attitude, and Tyzzier has advanced evidence in favor of the hereditary influence on the causation of cancer.

Paine (Lancet, Oct. 20, 1920) believes that a hereditary predisposition to cancer may be shown by the fact that cancer occurs earlier in those who have a familial history of cancer than in those who do not have such a history.

Irrespective of heredity there seems to be a certain constitutional change or predisposition to cancer production. This is exemplified by the fact that an irritation may be to all appearances the same in two persons, yet in one cancer follows, while in the other there is no change. The cause of this predisposition is difficult to define. It may be due to metabolic changes either resulting in general cellular inferiority or growth inequilibrium, so that what would normally be inappreciable factors result in unregulated reproduction.

Opitz believes that there is a hereditary disposition not only to cancer in general but to cancer in particular organs. He thinks, however, that it plays a minor rôle, and that hereditary influence is present in 10 per cent., or at the highest in 20 per cent., of all cancers.

The factor of heredity in experimental tumors seems to be illustrated in the work of M. Slye (Surg., Gyn. and Obst., Aug., 1921), who found it possible both to produce mice with a high incidence of tumors and to obtain strains of mice with a tendency to grow certain kinds of tumors, e.g., sarcoma, or tumors of certain organs, such as the liver, lung, or mammary gland.

In a study from the Netherlands

Cancer Research Institute, dealing with a large number of clinical cases, Wassink and Van Raamsdonk (*Néoplasmes*, Aug., 1923) demonstrated a familial predisposition to cancers of varying locations in 13 to 39 per cent. of various types of cases and a predisposition on the part of a certain organ in 9 to 39 per cent. Reference is made to Slye's research as having apparently determined that cancer heredity is a recessive quality. For this reason, one always observes less evidences of heredity than actually exist.

The recessive character of cancer is illustrated in 12 families traced for 4 or 5 generations by the writer, indicating that the occurrence of cancer is more familial than hereditary. Thus, in 1 family no cases of cancer were known in the 1st generation, but there were 15 in the 2d; 6 in the 3d, which had 3 or 4 times as many members as the 2d, and none in the 4th. Inter-marriage with a cancer family was not followed by development of cancer with any regularity. J. van Dam (*Nederl. Tijd. v. Gen.*, Jan. 5, 1924).

Bullock and Curtis (*Jour. of Cancer Res.*, viii, 446, 1924) have demonstrated the hereditary transmission of liver sarcomata.

**Exciting Cause.**—Of all the factors related to the causation of cancer the most important is, undoubtedly, the question of the existence of a possible exciting cause of its growth.

For a long time a relation between *trauma* and cancer has been recognized by many. In this country Phelps has maintained that there is no connection between trauma and cancer.

Of 115 authors whom he has consulted, only 7 have admitted a connection between trauma and the occurrence of carcinoma; 27 limit such a connection to trauma in the form of persistent irritation; 37 to trauma

limited to some form of chronic inflammation; 11 have excluded all forms of trauma as having any etiological connection with carcinoma; 12 have admitted the connection of an undefined trauma with cancer; 10 make no mention, however, of trauma as an etiological factor; 9 mention exclusively intrinsic factors in discussing the cause of cancer, and 2 confess ignorance of the etiology of cancer.

Phelps made an extensive review of the literature upon this subject and found that there were 3000 books and articles written upon the connection of trauma and the development of cancer, but, notwithstanding his extensive study, he believes there are *only 3 cases in which the connection of the trauma in development of the cancer is sufficiently intimate to allow of a connection between the two*. In 2 of these instances cysts seem to have been present in association with the carcinomatous deposits, and the history of the third case merely states that an elderly lady was struck on the back by a tennis ball and where the ball struck her there formed a large and rapid-growing carcinoma.

There seems to have been no microscopic examination made in this case, and Phelps concluded, therefore, that the evidence of a relation between trauma and the development of cancer is insufficient.

There is much to be said, however, in support of Coley (*Annals of Surg.*, liii, 449, 1911), who considers that there is an etiological connection between trauma, at least in its broadest sense, and cancer. Coley stated that in 9 of 46 cases of sarcoma which he had previously reported the tumor developed within one week after the injury and at the exact site of the injury. Since this report he had observed 800 cases, making a total of 970 cases of malignant disease. Of the 970 cases a definite history of trauma existed 225 times, or in 23 per cent. In 117 of the 225 cases, or in 52 per cent., the tumor developed within one

month after the injury. Coley also has observed carcinoma of the breast following injury within one week's time in 5 cases; two weeks to a month's time in 14, one month to two months' time in 3, two months to six months' time in 8, six months to twelve months' time in 7, one year to two years' time in 5, two years to three years' time in 3, and over three years' time in 7, cases.

Unquestionably the closest relation has existed between injury and the development of certain melanotic sarcomata from pigmented moles. Of 250 cases of carcinoma personally observed by Coley there was a history of antecedent trauma in 82, or 32.8 per cent.; 120 of these were carcinomata of the breast. Other statistics have contradicted these high figures. Thus, Machol (In. Diss., Strassb., 1900) gave 2.06 per cent.; Wolff, in 1874, 14.35 per cent.; Liebe, in 1881, 10.87 per cent.; Wuerz, in 1900, 5 per cent., and Serdener, in 1909, 14.19 per cent. (Mock and Ellis).

McWilliams has reported 100 cases of carcinoma of the breast, of which 29 had a distinct history of antecedent trauma.

E. Rose (Beitr. z. klin. Chir., cxxxiv, 244, 1925) has reported 3 cases of cancer of the breast following paraffine injections for cosmetic purposes.

Segond has formulated a law that, in order to have a knowledge of the relationship between trauma and carcinoma scientifically acceptable, there should be evidence of a medical examination prior to the injury. In 4 of Coley's sarcoma cases such evidence existed. Coley has also observed 3 striking cases of internal cancer. In cases of sarcoma, Sands states that there should probably be an interval of

*three weeks to one year*, and in carcinoma an interval of *six weeks to one year* between the time of the receipt of the injury and the development of the new growth.

Coley's conclusions are that a local trauma of any kind, from chronic irritation to a single contusion, is frequently the exciting cause of malignant tumors of all types. That a single local injury may be the cause of a carcinoma or a sarcoma is no longer questioned. This relation in no way depends upon our ability to offer an explanation of the same, nor on the acceptance of any one of the various hypotheses as to the etiology of cancer.

Ziegler (Münch. med. Woch., xlii, 621, 1895) gave 170 cases of carcinoma, of which 37, or 22 per cent., had a history of trauma. In 171 cases of sarcoma 35 were associated with a single trauma. He reported on 750 collected cases and 50 observed at the Pathological Institute of Munich. In 358, or 44.7 per cent., of these cases cancer was associated with trauma, and in 316, or 39.5 per cent., of the cases sarcoma was associated with trauma. The time varied from almost at once to forty-nine years.

Wilson and Willis (Jour. Amer. Med. Assoc., lv, 921, 1910) reported that 167 carcinomata of the lip, 46 of the mouth and tongue, 2 of the esophagus, 189 of the stomach, 15 of the gall-bladder, 22 of the appendix, 20 of the colon, 42 of the large gut, and 57 of the rectum were subjected to microscopic examination for information as to the starting point of the growth. Evidence of the previous existence of a chronic inflammatory process was found in 30 per cent. of the lip cases, 67 per cent. of the stomach cases, 33 per cent. of the gall-bladder cases, 100 per cent. of the appendix cases, 10 per cent. of the colon cases, 40 per cent. of the large-gut cases, and 3 per cent. of the rectum cases.

Bloodgood (Jour. Amer. Med. Assoc., Dec. 27, 1913) was unable to find a single case with a well taken history, in 820 pathologically fully developed cancers of the skin and mucous membranes, which showed

the absence of a previous defect which might be looked upon as a precancerous lesion.

Others believing in trauma as a cause of cancer are: McWilliams (Med. News, Apr. 28, 1909); Von Bergmann (Med. Woch., 1, 137-139, 1901); Roske (Habit. Schrift, 1901); Murphy (Jour. Amer. Med. Assoc., viii, 985, 1094, 1176, 1254, 1345, and 1428, 1912); Ziegler (Münch. med. Woch., 895, p. 621); Lowenthal (Arch. f. klin. Chir., 1-101); Von Graefe (Centr. f. d. Grenz. d. Med. u. Chir., Nov. 28, 1913); G. Villata (Policlinico, xxxii, 451, 1925).

That acute, as well as chronic, traumatism or irritation may lead to cancer is suggested by a case concerning a man aged 22 who had been shot in the hand at a point where a pigmented wart existed. After healing, recurrent warts developed at that point, in spite of repeated cauterizations and surgical removal, and eventually, about 3 years after the injury, a carcinomatous growth was produced. The original trauma is thought to have displaced the wart cells, and irritation led them to atypical proliferation. E. Langer (Dermat. Zeitschr., Jan., 1922).

G. Villata, in his studies of cancer, found that 8 per cent. of 127 sarcoma cases and 5.19 per cent. of carcinoma patients gave a history of a single severe trauma as having a causal relationship to the cancer. He thinks that trauma undoubtedly favors production of cancer in the injured tissues, but is never directly responsible for the malignant growth.

In regard to *trauma in industrial insurance*, H. E. Mock and J. D. Ellis (Jour. Amer. Med. Assoc., Jan. 23, 1926) have reviewed the question of trauma as a cause of tumor formation. This is of the utmost importance, because of social legislation in the form of compensation laws which have been enacted in the last 20 years. Mock has evolved the following procedure as guidance for compensation boards in cases

where trauma is considered as the cause of a malignancy:

1. There must be reasonable proof of a trauma of sufficient seriousness to cause definite tissue changes.

2. The developing neoplasm must be at the same site as the original injury and must involve some of the tissue which without reasonable doubt could have been involved in the original trauma.

3. Definite evidence must be produced to prove that no neoplasm existed at the site of injury prior to the accident.

4. In addition to the trauma there must be definite bridging signs, such as a persistent swelling over unhealed wound or anatomical or functional disturbances which connect the trauma with the malignant growth; subjective symptoms, such as complaint of pain, tenderness or weakness, are impossible to evaluate or visualize and therefore must not be considered competent evidence.

5. It is safe to say that a malignant tumor which develops within two weeks after the trauma existed prior to the injury.

Cancer in *scars* following traumatism inflicted on the tissues either from without or within arises as follows: The contraction of the scar partly cuts off the circulation from the local cells, causing them to revert to a less differentiated, more embryonal type. After the lapse of some time and the application of trauma to the cicatrix, its cells, which have acquired a greatly increased faculty of proliferation on account of their embryonal retrogression, begin to divide, cancer resulting. A factor in prophylaxis is, therefore, to avoid sources of injury to the skin, alimentary tract or other organs, or, if scarring already exists, to protect it against injury. A. Lumière (Néoplasmes, May-June, 1923).

Haberfeld (Zeitschr. f. Krebsf., vii, 190, 1908) discussed the question of the connection between chronic inflammation of the stomach, gall-bladder, and lungs and the incidence of carcinoma. He based his statement for the stomach upon autopsies of 662 cases of gastric cancer; 106, or 16 per cent.,



were found in which, as far as microscopic appearances showed, the disease originated from ulcer. Häberlein considers that 7 per cent. of ulcers of the stomach undergo malignant transformation, while the Mayo Clinic believes that there is evidence, in the microscopic sections of 70 per cent. of gastric cancers, that the latter have originated in ulcer. Habersfeld found stones 119 times in 164 primary cancers of the biliary passages. Evidence of the relation of chronic irritation to cancer of the lung is less striking. Three cases have been reported in which primary cancer of the lung was associated with tuberculosis.

Vaselin employed as a vehicle for drugs such as camphor in subcutaneous or intramuscular injection is capable of giving rise to serious tumors in the tissues. In 7 such cases witnessed the tumors developed where injections of camphorated oil had been made, and only after an interval of about 5 months to 2 years. The tumors appear to have a marked tendency to recurrence and give rise to metastases. The authors term them vaserinomatata. In the 7 cases reported the tumors were removed, but in all cases recurred. A wide resection, as in a malignant tumor, seems necessary. Jacob and Fauré-Fremiet (*Rev. de chir.*, liii, 221, 1917).

Tar and mineral oils, when in contact with the skin, tend to occlude the orifices of the skin glands. This may be followed by irritative follicular or ostiofollicular lesions of the acne type, and may result in multiple flattened or exuberant horny formations, at times like cornu cutaneum. These tumors are for the most part benign, remain small, and may ulcerate, later healing spontaneously. Some, however, pass into large ulcers and require surgical treatment; they may even become generalized and cause death. The lesions develop particularly on the forearms and face. They may, however, occur on the covered parts, exposed to accidental con-

tact of the noxious materials. The condition occurs only in workers who have been exposed a number of years. Lack of cleanliness is a favoring influence. Proper care of the skin is the main factor of safety. G. Thibierge (*Bull. de l'Acad. de méd.*, Aug. 20, 1918).

Heat as a cause of cancer is illustrated by the cancers occurring among the natives of Kashmir who, during the cold weather, wear on the abdomen a basket filled with burning charcoal. Of 496 epithelial cancers between 1890 and 1899 at the Kashmir Mission Hospital, 363 were Kangri-burn cancers (Neve, *Indian med. Gaz.*, May, 1902).

Again, cancer of the mouth is very common in India, where the betel-nut is extensively chewed; 411 of 976 carcinomas treated in the Madras General Hospital between 1892 and 1901 were in the mouth (*Indian Med. Gaz.*, Apr., 1902).

Investigation of coal, tar, pitch, soot, naphthalene, etc., aniline dyes, petroleum, grease, tobacco, betel-nut, Röntgen rays and radium rays, arsenic and manure as causes of cancer. The investigation showed that mechanical injury *per se* can play only a minor part in the predisposition to occupational cancer. All the agents seem to bring about the predisposition to malignancy in a somewhat similar manner, *viz.*, by becoming impacted in the tissues, where, by giving rise to cell proliferation, they produce a warty condition, then a sore with epitheliomatous margins.

All of the active commodities examined were products of, or are derived from, the products of the death and decomposition of living matter. Carcinoma seems more frequent, in general, at sites continually subjected to organic matter undergoing bacterial decomposition, such as the rectum, stomach and intestinal tract, mouth, uterine cervix, breast, prepuce, anus, scrotum, etc. Decaying organic matter of all descriptions fertilizes living matter, and promotes cell pro-

liferation. Probably the mischievous agents are organic nitrogenous substances of a group common to all the dangerous commodities. The name auxetics is given to these cell-division-producing agents. H. C. Ross (*Jour. of Cancer Research*, Oct., 1918).

A great impetus to the study of cancer was given by the report of Yamagiva's success in producing carcinoma on the ears of rabbits by long repeated injection with coal tar. (Yamagiva and Itchikawa, *Jour. of Cancer Research*, iii, 1-29, 1918). Attempts to produce cancer by injection beneath the skin or irritation by rubbing irritating substances on the surface had already been made in a desultory manner by different experimenters.

In 1906, B. Fischer (*Munch. med. Woch.*, liii, 2041, 1906) introduced olive oil saturated with Scharlach R under the skin. Growth of adjacent cells occurred and resembled cancer. After the oil was absorbed the growth stopped. In 1907, F. Renke (*Deut. med. Zeit.*, xxviii, 579, 1907) introduced 4 per cent. solution of ether into the eye of a salamander, thus producing typical growths. Solution of growths injected or transplanted into peritoneum of other salamanders grew for some time. The growths resembled carcinoma. In 1909, M. Askanazy (*Wien. Med. Woch.*, lix, 2517, 1909) added ether to embryonic tissue. Injections of this tissue grew more rapidly than without ether. In 1918, Tsuitsui transformed a benign tumor of white rats into a malignant tumor by using Sudan III in olive oil, a drop at a time, at 5 or 6 day intervals. The tumor was successfully transplanted through 14 generations. Lipschutz (*Wien. klin. Woch.*, xxxiv, 613, 1921), a diligent worker, produced wart-like nodules by injections

of coal tar. The transplanted tissue produced warts, though the tissue transplanted was completely absorbed. Vielman (*Nederl. Tijdschr. v. Geneesk.*, xx, 2398, 1921) also was able to transplant and grow irritation cancers in the mouse by tarring. The growth occurred in 3 to 18 months (average, 6 to 9 months). Scarification with the tarring hastened the onset (Murray, *Imperial Cancer Research Fund*, 1923). It has also been found that rats and mice are probably more susceptible than rabbits. The sex of animals has no influence.

In 60 mice, the author painted a line of tar on alternate days from the neck to the tail; 240 days later there had resulted 23 cancers and 16 benign tumors. In 19 mice the tumors were multiple—usually cancerous—and in 20 single. The varying results under identical conditions lead him to emphasize the factor of individual susceptibility. Some individuals are immune, others predisposed to benign growths, and others still, to malignant. The benign tumors, it would seem, may represent a half way point on the path to malignancy. G. Roussy (*Bull. de l'Acad. de méd.*, June 6, 1922).

Constitutional predisposition before irritation is necessary before a growth can be produced, according to Bullock, Rhodenburg, Lipschutz, Maisin and G. Masse (*C. r. Soc. de biol.*, xciii, 449, 1925).

Leitch thinks that some change is produced in the cells by tar irritation. This change is not detected by the microscope. Cancer evidently is not induced by any specific substance in coal tar, as many chemical substances may induce such changes, especially lipid solvents.

In rabbits in which cancroids on the ear were induced by tar, crude paraffin oil, etc., it was observed that swelling, inflammation, and microscopically carcinomatous nodules were

more pronounced and appeared more quickly in animals given *cholesterol* in addition to the ordinary diet than in controls. M. Borst (Zeit. f. Krebsf., Aug. 26, 1924).

A peculiar fact noted by Staehelin (Klin. Woch., Sept. 24, 1925) was that there was an increased frequency of primary cancer of the lung since 1912 in Basel, Switzerland, while the general incidence of cancer in the same city had not increased. He thinks this increase may have been due to the tarring of the streets.

Experiments showing that *refined mineral oils*, such as are used for machine lubrication, are capable of producing skin cancer after long exposure, and which support the contention of Southam and Wilson that mulespinner's cancer of the scrotum is due to several years' contact with lubricating oils. A. Leitch (Brit. Med. Jour., July 7, 1923).

In a series of experiments illustrating the *cumulative action* of irritations inducing cancer, there was noted a marked uniformity in the number of applications of tar to the ears of white mice required before the 1st visible evidences of change in the tissues appeared, irrespective of the intervals between the applications. Thus, 22 applications were required when made at 2-day intervals, and 18, when made at 7-day intervals. On the other hand, once this stage of initial visible change was reached, a malignant aspect developed in a definite further period of 50 to 60 days, irrespective of continuance of the irritation. Deelman (Nederl. Tijd. v. Gen., July 26, 1924).

Narat states that cancer may be produced in animals by irritation with many substances, *e.g.*, caustic potash, 3 to 6 per cent., or hydrochloric acid, 3 to 5 per cent. One of these agents was applied at regular intervals of 2 days till microscopic lesions appeared, then twice weekly.

Tar attracts cells to it and away from

the skin blood-supply. According to Burrows, it destroys a substance formed by the cells which is a stimulating substance for growth of the cells. The action of coal tar is purely physical. Other oils, such as corn oil, will produce the same results as coal tar and, as Jorstad remarks, "it is very improbable that corn oil contains chemically active substances similar to coal tar, while it may have the same solvent action."

Davidson (Jour. Path. and Bact., xxviii, 621, 1925) found that rabbits on whom coal tar had been applied to the ear to cause cancer suffered from cirrhosis of the liver.

Endorff, in Fibiger's laboratory, produced adenocarcinoma in the mammary gland of a mouse by injecting minute quantities of tar over long periods. This was the first adenocarcinoma to be produced by this method. Rats and mice are more susceptible than rabbits.

In 1912, Fibiger had reported the finding, in the stomach of rats, of tumors which resembled malignant growths and were due to the irritation produced by a small parasite known as *spiroptera*. A part of its life cycle was spent in the cockroach. This discovery of Fibiger enormously stimulated cancer research, and renewed endeavors to ascertain its cause.

Tobacco has long been considered a causative factor of cancer in the human mouth, but it has been impossible to cause cancer in animals by use of it. Leitch (Brit. Med. Jour., July 27, 1923).

Narat (Jour. Cancer Res., ix, 134, 1925) thinks that possibly metabolic, endocrin or vegetative nerve disturbances play an important rôle in the origin of cancer, whether the irritant be of a physical, chemical or patho-

logical nature. Age and sex do not seem to have much influence.

The relationship between cancer and *endocrin disease* emphasized. Very often before cancer appears, and always after, the patient shows unmistakable symptoms of dysendocrinism, which thereafter become more pronounced. These symptoms are: (1) High blood-sugar ratio, with or without (usually without) glycosuria, and (2) abnormal pigmentation. High blood-sugar ratio without glycosuria often means beginning diabetes; perhaps oftener, after the age of 50, it means beginning cancer. Skin pigmentations seem to be normal old-age phenomena, but an abnormal or unusual pigmentation always suggests ductless glands to the clinician, and also frequently precedes by several months the appearance of cancer, though not always a skin cancer. S. W. Little (Med. Rec., Apr. 8, 1922).

Data bearing on the relationship of endocrin influences to cancer were afforded by experiments on a transplanted rabbit tumor. In *thyroidectomized* animals the tumor grew steadily and rapidly. Where the thymus was removed it grew slowly, as in old animals. After partial thyroidectomy, the tumor at first grew rapidly, but was brought under control. After complete thyroidectomy very widespread metastases occurred in all cases, this operation increasing malignancy. W. H. Brown, L. Pearce and C. M. Van Allen (Jour. Amer. Med. Assoc., June 30, 1923).

Arguments supporting a connection between *involution of the sex organs* and cancer production. Many women with carcinoma exhibit stigmata of virilism, such as hypertrichosis, and in pseudohermaphrodites tumors are very common. H. Auler (Zeit. f. Krebsf., May, 1924).

Of great significance, in its relation to the exciting cause, is the difference in the frequency with which various portions of the body are affected among different races. In England and Wales, out of 10,000 deaths from

cancer, there were, among the males, 926 due to cancer of the lip, tongue, or buccal cavity, and 148 due to cancer of the penis and testicles. There were among females 2259 due to cancer of the uterus, 1656 due to cancer of the breast, and 83 due to cancer of lip, tongue, or cheek.

In the whole of India, among 10,000 deaths from cancer among males in the English hospitals, cancer of the penis and testicles was twice as frequent as in England, and cancer of the lip was three times as frequent. Among the females, cancer of the uterus was one-half as frequent as in England. Cancer of the breast was observed three times as often, while cancer of the lip was four times as frequent.

The fact which we are attempting to develop becomes still more evident when we compare the frequency of the various forms of cancer among the natives of India with its frequency among the English residents living beside them. Cancer of the penis and testicles is ten times as frequent among the Indians, while cancer of the lip, cheek, and tongue occurs about in the same proportion. Among females the frequency of cancer of the uterus and breast does not show any great difference between the two races. On the other hand, cancer of the lip and tongue among Indian women is six times as frequent as among the English women.

The irritation factor in cancer is illustrated in the fact that the condition occurs almost exclusively in portions of the body exposed to the irritation of the outside world. This includes the gastrointestinal canal, which comes in contact constantly with filthy food in locations in which stasis insures long continued irritation. A notable example is found in the enormous incidence in people eating raw vegetables fertilized with manure. Thus,

the Japanese suffer greatly from cancer of the stomach, while the Hindoos, whose religion requires boiling of food and drink, are notably free from it. A. J. Ochsner (Med. Rec., Feb., 1921).

The boiling of water used for drinking, washing, and bathing would prevent the disease. In the states in which cancer is most prevalent there is more stagnant water in which maximum numbers of protozoa are to be found. Cancer incidence varies about inversely with that of typhoid, a water-borne disease due to pathogenic bacteria. Where protozoa predominate it appears probable that they have destroyed the bacteria. J. W. Shannon (Boston Med. and Surg. Jour., May 19, 1921).

The significance of these facts is very great. The excessive frequency of cancer within the mouth among Indian and Ceylonese women is accounted for by the irritation produced by the chewing of betel-nut, just as the striking contrast between cancer of the lip, tongue, and cheek in English men and women is directly due to the use of tobacco by the former. The greater frequency of cancer of the penis and testicles among Indian men as compared to the English is undoubtedly due to their uncleanly habits and the absence of circumcision. This is made still more evident by the almost entire absence of cancer of the penis among the circumcised Moham-medans, who have lived for generations close together with the other inhabitants of India. Another fact of importance is the great frequency of cancer of the abdominal wall among the natives of Kashmir, while cancer occurring in this locality is almost unheard of among Europeans. The explanation is found in the fact that in Kashmir the natives irritate the abdominal wall by wearing upon it a charcoal oven, the irritation thus produced being responsible for the cancer.

These facts are important because we may almost say that in them we have control experiments demonstrating the direct connection between chronic irritation and the incidence of cancer. Less marked evidence of the same facts, but still of very great importance, is the frequency with which cancer of the stomach is preceded by ulcer; cancer of the biliary passages by the history of chronic cholelithiasis; cancer of the breast by mastitis, and cancer of the cervix uteri by the history of cervical laceration and erosions; also the association of bilharzia hæmatobia with cancer of the urinary tract, and the frequent implantation of cancer upon tuberculous and syphilitic processes.

While no definite opinion as to the nature of cancer can be found from these data, they demonstrate at least that no one etiological factor is constantly associated with the disease, but that a great variety of conditions precede it, and such evidence points to the conclusion that cancer is to be considered as a pathological disturbance of the normal cell life.

The possible factors of cancer enumerated as follows: External stimulation, mechanical or chemical; internal chemical stimulation, especially through internal secretion; heredity, including various not yet well defined factors, some probably identical with other causes; embryonal character of tissue or disturbances of embryonal development, including parthenogenetic development of the ovum; in an indirect way, age; contact between normal and cancerous tissue; a possible effect of micro-organisms. Cancer is in all probability usually due to changes in cell metabolism which are of such a nature that they propagate themselves. Leo Loeb (Amer. Jour. Med. Sci., June, 1920).

Cancer conceived as a blood disease due to *persistent autotoxemia*. The can-

cer cells thrive only on a vitiated soil, in this instance the blood. Fungi likewise thrive only on a polluted soil. So long as the thyroid gland is healthy, healthy cell metabolism will continue; if it receives toxic blood, however, its functional activity will be reduced, and so we invariably find *hypothyroidism*. Moreover, there is actual atrophy of this gland in cancer subjects. Robert Bell (Med. Rec., Feb. 28, 1920).

Evidence presented of a change of the intestinal chemistry in cancer which is not secondary, but precedes the development of the tumor and persists even after radical operation. Freund and Kaminer (Wien. klin. Woch., Dec. 6, 1923).

Cancer is, with rare exceptions, as much one of the results of *chronic intestinal stasis* as are appendicitis, colitis, diverticulitis, gastric and duodenal ulcer, etc.

The writer describes a series of changes spreading through the alimentary tract, with impaired fecal flow and inflammation of mucous membranes, with resulting absorption of poisonous material and fouling of the nutritive supply all over the body. An excessive strain is meanwhile thrown on the ductless glands, which hypertrophy at first, but later degenerate and atrophy. The frequency of cancerous changes in the breast and ovary is ascribed to the early cessation of functional activity of the sex organs in the female. Cancer never attacks a healthy organ or tissue. Sir W. A. Lane (Pract., Apr., 1924).

**Influence of Occupation.**—Certain occupations predispose to cancer; chimney sweeps are particularly predisposed to cancer of the scrotum and groin. Very few statistics upon the influence of occupation are available. Those of McConnell (Zeit. f. Krebsf., vii, 238, 1908-09) will serve our purpose as well as any.

For each 100,000 of population according to occupation (males, except as noted):—

Laborers .....	126.6
Sailors and fishermen .....	113.1
Smiths .....	107.3
Nurses and midwives .....	105.0
Clergymen .....	102.2
Servants (female) .....	99.6
Masons and stonecutters .....	98.0
Builders, planters, and country laborers .....	87.7
Merchants and storemen .....	81.3
Gardeners and florists .....	72.9
Upholsterers .....	72.6
Country occupations, transport and other occupations in open air ....	69.2
Physicians .....	67.5
Porters .....	66.7
Working and serving class .....	66.5
Dealers and peddlers .....	62.7
Police, nightwatchers, and detectives .	60.3
Hotel and pension officials .....	60.1
Tailors .....	58.4
Cashiers, auctioneers' agents .....	58.1
Manufacturers and mechanical industries .....	53.3
Lawyers .....	52.5
Machinists .....	52.2
Merchants and storekeepers .....	52.0
Students, professors, etc. ....	51.7
Bakers and chefs .....	51.0
Teachers (female) .....	47.8
Stablemen .....	46.1
Painters .....	45.0
Men servants .....	44.3
Public servants, police and military ..	42.9
Bank officials .....	41.4
Woman tailors and dressmakers ....	38.4
Office help .....	37.3
Hotel men .....	35.3
Weavers .....	34.5
Mountain dwellers and quarrymen ...	33.4
Iron and steel workers .....	31.5
Bookkeepers and correspondents ....	28.0
Café and restaurant keepers .....	28.0
Washwomen .....	25.3
Carters, threshers, guides .....	22.6
Bookkeepers and accountants (female) .	15.1
Workers in various textiles (female) .	9.9

The table is given for what it may be worth, but in drawing conclusions from it one must make allowances for inaccuracies incidental to data of this character.

**Diet.**—Little may be said upon the

relationship of diet to cancer. No one form of diet has ever been found to influence the progress of the disease in the slightest degree. In general, it is assumed that those living upon a vegetarian diet are to some degree immune from cancer. This view is based entirely upon the supposed infrequency of cancer in China, Africa, and southern countries in which a vegetarian diet is more universal. In discussing the geographical distribution of cancer we have shown that other factors should influence our conclusions in this matter.

In general, the whole subject, particularly in our present state of ignorance as to cancer metabolism, rests upon too uncertain a basis to permit of even general deductions.

It has been frequently stated that there has never been recorded a case of direct transmission of cancer from a patient to an attendant. This is apparently controverted by a report in the *Journal of the Amer. Med. Assoc.*, Nov. 14, 1925 (letter from Paris), in which it is stated that H. Zeadon, an interne in Paris, pricked the finger of his left hand while puncturing a lymphorrhagic effusion in a patient operated on for cancer of the breast, and at the site of the puncture there developed an ulcerous skin lesion which it was impossible to heal. The true nature of the lesion was only discovered upon histological examination of an enlarged gland which had been removed from the axilla; the disease progressed so quickly that disarticulation of the shoulder was necessary. This direct transmission or transplantation of the cancer-exciting principle would seem to bear out in some manner the possibility of a parasitic origin of cancer; or else, it would indicate that there is a direct transmission of an elemental substance, possibly of a ferment nature, so powerful that a small amount carried by the needle into the finger was sufficient to initiate cellular changes which led to unregulated cellular proliferation in the form of a cancer.

**THE ESSENTIAL NATURE OF CANCER.**—Of the various theories which attempt to explain the nature of cancer, the **parasitic theory** is entitled to discussion first. Aside from some clinicians who have not extensively familiarized themselves with the pathology of cancer, and a comparatively few pathologists, the parasitic theory has few advocates. In many features cancer is unlike any known form of infectious malady. In estimating the importance of the supposed parasites we may first state that none of them have been constantly found, nor fully confirmed, by other observers. Most of the supposed protozoön forms owe their existence to the innumerable products of intracellular degeneration. Tumor-cells will withstand exposure to solutions of bichloride of mercury and cyanide of potassium to a degree that any known pathological bacterium or spirocheta cannot endure. Well-authenticated cases of the transfer of a malignant tumor from one human being to another are practically nonexistent. The few instances of such a nature which are quoted are not beyond criticism, and are so few that there is no support for the parasitic theory from this standpoint.

The clinical course of cancer is, also, evidence against the parasitic hypothesis. Its spontaneous development from normal tissue; the multiplicity of the forms of chronic inflammatory processes which bear an etiological relation to it; the formation and growth of metastases, and the different character of the immunity in cancer among the lower animals from the immunity occurring in any known form of infection, all indicate that cancer is not caused by a specific pathogenic organism.

Yet, in spite of the view held by the majority of pathologists that cancer is not or cannot be due to micro-organisms, there have not been lacking numerous workers who have spent years of effort in attempting to isolate micro-organisms, to culture them and by inoculation of them to produce cancer. Among such workers may be mentioned Scheuerben, Doyen (micrococcus neoformans), and, more recently, Nuzum, Glover, Blumenthal, Young, and Gye and Barnard, of London. The latter have isolated an ultra-microscopic filtrate which they consider the cause. None of these organisms, however, fulfill all the postulates which are necessary to prove a cancer organism as the cause of cancer. Prior to this time, however, it had been proved that the chicken sarcoma of Rous contained a virus which could pass through a Berkefeld filter and after inoculation into a rabbit could reproduce itself. Pentimalli demonstrated that the action of this virus could be localized to an area which had been subjected to irritation; for instance, after injection of the virus into the circulation of a chicken, he found that irritation of the chicken's comb would induce a tumor in the area of irritation. If, however, more than five days elapsed from the time of injection to that of the irritation, no local growth

occurred; evidently in this time a destructive or resistant substance had been formed against the virus.

Blumenthal and his associates isolated from carcinoma lymph 10 organisms which apparently are able to produce tumors. F. Reichert (Zeit. f. Krebsf., xxii, 446, 1925) states that on March 2, 1925, before a scientific association in Dresden, he announced the news that bacteria may carry an ultra-visible virus which may be the active incitor of the tumor.

In the Lancet for July 18, 1925, Dr. W. E. Gye and Mr. J. E. Barnard, F. R. S., reported the discovery of a minute organism which is filtrable through a Berkefeld filter but visible in an ultra-microscope developed by Mr. Barnard.

It is thought that the virus which resides in the cells of the body requires some activating principle, probably specific, necessary either to combine with the cells before they are attacked by the cancer virus or else something of a chemical nature to combine with the virus before it is able to influence cell growth. The activating substance is obtained in the supernatant fluid after centrifuging at high speed an emulsion of tumor, or by treating a tumor with chloroform. The reaction is expressed as follows:

Unactivated virus



plus

Specific activating chemical substance which is thermolabile

equal

Activated virus



plus

Normal cell

equal

Cancer cell

Unactivated virus



plus

No activating chemical substance

equal

Unactivated virus



plus

Normal cell

equal

Cancer cell



*Possibilities of Derivation of the Activating Substance.*—Firstly, something contained in embryonic tissue. This something is in the nature of a ferment, for the activating substance must be either in the ovum or the spermatozoa, or else is the result of their union. This, however, is hardly possible, for if such were the case, the disorderly and undifferentiated growth of the primitive layers would be interrupted in early fetal life by the production of bastard cells. This does not occur. The principle, whatever it may be, is formed later in fetal life. The growth-stimulating substance which is necessary to carry on indefinite tissue culture *in vitro* is found in embryonic tissue, and without this substance continuous culture of tissue cannot be accomplished.

It is likely that this principle is formed in later adult life and has something to do with the disintegration of tissue cells. Rhoda Erdmann showed in her culture of epithelial tissue cells that connective tissue has a permanent influence on the cultural growth of such cells, and that in the absence of connective tissue the cell will not grow. Here a new factor may enter; the substance which is freed in the death of tissue cells may combine with something in the connective tissue which renders it activating for the epithelial cell.

It is a pertinent fact that neither the epithelioma nor carcinoma develops in the absence of connective tissue. The activating principle may be either a substance from disintegrating cells or a substance from connective cells. Supporting this hypothesis is the fact that cancer occurs most frequently, if not constantly, as a consequence of chronic irritation.

From experimental evidence the writer holds that malignant cells continuously secrete a growth-stimulating principle. Normal cells do not have this except when, after injury, they seek to regenerate themselves. This may explain the relationship of prolonged irritation to cancer growth. Drew (Brit. Med. Jour., July 28, 1923).

The views of Gye and Barnard have received considerable publicity. The consensus of opinion is that while their work is interesting and most important from the point of view of fundamental knowledge of malignant tumors,

their findings to date furnish us with additional knowledge concerning the biology of merely one very unusual tumor type. Editorial (Boston Med. and Surg. Jour., cxiii, 429, 1925).

The results obtained by Gye and Barnard, if they should be confirmed, apply only to sarcoma; for epitheliomas the problem remains unsolved. Roussy (Jour. Amer. Med. Assoc., Sept. 19, 1925).

Regarding the *spontaneous development of cancer from normal tissue*, the transition from the normal skin-cells into tumor-cells in some of the earliest growths, particularly in minute cutaneous epitheliomata, is so gradual, and the absence of any chronic inflammatory process is so manifest, that the direct derivation of the young tumor from the normal cells by a primary metaplasia of the latter seems clear. The great variety of chronic inflammatory processes which may precede cancer demonstrates that no one specific form of inflammation is connected with its development, such as we would expect if cancer were dependent upon a specific form of parasite.

The formation of metastases always occurs by the sweeping away in the blood-stream of minute particles of tumor-tissue and the subsequent lodging of these in some distant portion of the body, where growth is really the result of an implantation. The surrounding cells, even when of the same nature as those in which the tumor has originated, do not always participate in the process; we should expect such a participation were cancer due to a parasitic organism.

A degree of protection against the inoculation of cancer can be established among the lower animals, but the character of this immunity is different from that belonging to any form of infection depending on pathogenic organisms. Animals displaying a marked degree of

natural immunity to the inoculation of virulent tumors may spontaneously develop tumors. The products of the disease do not uniformly confer immunity.

Woglom (Jour. Cancer Research, June, 1925) states that receding Jensen rat sarcoma as compared with the growing tumor begins to fall behind in proliferating energy about the tenth day. Spontaneous immunity seems to be engendered in the host. The periphery of the receding tumors is first attacked by some deleterious principle or product of the host. Necrobiosis, followed by a fibrosis, passes in from the periphery and the tumor is gradually absorbed and converted into a fibrous nodule.

The author reports having obtained an organism with a complex life history almost constantly from cancer. It is credited by him with yeast, coccid, bacillary and amorphous phases. In the latter phase it lives in symbiosis with the cancer cell. It belongs to a type of bacteria that is widespread in nature, and tissue susceptibility, wherever it occurs, therefore involves prompt risk of infection with it. J. Young (Brit. Med. Jour., Jan. 10, 1924).

An anaërobic *diphtheroid bacillus* and a mannite non-fermenting *staphylococcus* were demonstrated in 15 cases of malignant disease, as well as *streptococci* in  $\frac{2}{3}$  of these cases. These bacteria are regarded as responsible for the tumor proliferation. W. M. F. Robertson (Lancet, Aug. 18, 1923).

From the extreme outer zone of 8 beginning human cancers, bacilli of the *B. tumefaciens* group were obtained. These organisms, when inoculated in plants, mice and rats, induced tumor development at the points of inoculation. In the rats these tumors could be cultivated through many generations, at times grew very large, and induced metastases. They were prone to recede, however, unless kieselguhr was added to the cultures. F. Blumenthal, H. Auler and P. Meyer (Zeit. f. Krebsf., Aug. 26, 1924).

The writer isolated a micrococcus in pure culture from 38 out of 41 early human breast cancers, from metastases in the axillary glands, and from metastatic growths disseminated throughout the body. It is identical culturally and morphologically with an organism previously isolated from the transplantable cancer of the mouse. It is cultivated in dextrose broth, with or without ascitic fluid. In early cultures its size averages 0.1 to 0.3 micron. It is extremely pleomorphic, and stains best by Gram's method or the Giemsa stain. Animals inoculated with it developed typical cancer and metastases, from which it could be isolated anew. In a patient suffering from a hopelessly inoperable cancer, repeated subcutaneous injections of the micrococcus in a distant part of the body produced a typical cancer. J. W. Nuzum (Surg., Gyn. and Obst., Mar., 1925).

Turning now from the parasitic theory to the **autogenetic theory**, one finds a conception which is far from complete but which, in its main outlines, seems to present a more satisfactory explanation of the facts surrounding the development of malignant disease. The theory has developed into somewhat different forms according to the stress laid upon two conceptions.

In 1865 Thiersch developed the idea of the difference in the length of life of the various tissues, and the effect upon one tissue of a disturbance in its relation to another. He maintained that the "rarefaction," to use his own word, of the connective-tissue stroma is responsible for the growth of cancer. His book is really the foundation of the autogenetic theory.

In 1877 Cohnheim described the existence within the tissues of *isolated groups of embryonic cells*, upon the discovery of which he elaborated the theory which bears his name. The hypothesis

is briefly as follows: During the period of fetal development, groups of cells become inclosed as isolated islands within tissues which are different in kind from those into which these cells should have normally developed; at some time later in life cancer develops from these isolated groups.

This theory is satisfactory from many standpoints. The Cohnheim theory supplies in the earliest stages not only the presence of isolated groups of cells in tissue of a different kind, but also the presence of a cell which has been set apart during embryological development. It requires only a small amount of imagination to suppose that such a cell is endowed with greater proliferative powers. Borrmann, from a study of 286 cases of young epitheliomata, concludes that all the complicated conditions necessary to explain the existence of groups of cells capable of unrestrained proliferation are fulfilled by the assumption of an embryonal inclusion. Borrmann may be said to represent the Cohnheim theory as it is.

The most important fact upon which Borrmann bases his conclusions is: The discovery of some *epitheliomata entirely buried within the corium* and presenting *no connection with any epithelial structure*. Mackwald, Tanberg, and Veit have described similar growths; Janeway met with two examples which strongly suggest such an origin, though at one point in each tumor there was a small connection with the epidermis. Further support is derived for the Cohnheim theory from the large class of *teratomata*, and from those *teratomata* in which the epithelial portions have undergone malignant change. The wide distribution of *chorioepitheliomata*, even occurring in the male, furnishes evi-

dence in support of the Cohnheim theory which can hardly be refuted.

To the minds of many, however, the Cohnheim theory does not furnish all that is needed to explain the origin of some cancers. The large amount of clinical evidence on the etiology of cancer above referred to; the possibilities of tissue metaplasia, and the very direct outgrowth of some cancers from the normal epithelial tissue, all point to other factors.

The facts relating to the inflammatory conditions preceding cancer, which Bashford has recorded, have demonstrated to him "that the different forms of irritation, although they have nothing in common, are of more moment than the sites in which they are applied, and are more or less out of accord with the hypothesis of a congenital origin as an explanation of all forms of cancer." Hansemann, Lubarsch and Benecke, and Krompecher have done much to develop the idea of cell metaplasia, and the important part which the epithelial cell itself plays in cancer development.

The view of Ribbert is deserving of special mention, as he undoubtedly represents most careful thought on cancer problems. He combines in a finished theory the essential ideas of Cohnheim and Thiersch, and his hypothesis may be stated as follows:—

The essential cause leading to the development of cancer is *an inflammatory process* surrounding the proliferating areas. By the products of such a process the *epithelial cells become separated from each other and from the single tissue of which they form a part*; they then begin their unrestrained proliferation. In the *majority of cases*, however, *it is an isolated complex of embryonal cells* which is so acted upon by the chronic inflammatory process.

It is difficult to believe that the ideas either of Ribbert or of Borrmann include all the factors demanded in the origin of cancer.

According to Janeway's hypothesis, the laws controlling the life growth and metaplasia of the normal epithelial cells themselves include, in many cases, all that may be needed for their transition into cancer. The transition into cancer must be regarded as of the nature of a *degeneration*, in virtue of which excessive proliferative powers replace normal physiological functions; this degeneration, in turn, is dependent at times upon the existence of previously isolated cell-complexes, at times upon inflammatory processes of the surrounding connective-tissue stroma, and, what is of more importance, at times upon no discoverable lesion external to the epithelial cells undergoing the transition into cancer. In cases of this last category the individuality of the cells of the organism is without doubt a determining factor.

Cancer is created in some manner by the division of *one cell failing to carry with it the centrosome*. The next division leaves it without control as a unicellular type of life capable of lawless growth more or less true to type but without a controlling brain. The cell becomes parasitic, and *primarily changes the local field into a slightly acid one* as an environment suitable for its growth. Ultimately this fluid permeates the body, a curious cancer cachexia occurs and with it there may be metastases later becoming manifest by growth at any point where cells may be carried. The resistant influence of youth may lie in the rapid reduction and restoration to normal of the acidity. The young cells have not exhausted the protoplasmic control bodies. In old age with hardening of the tissues, it is easier for a centrosome to be immature in its development and it may

wholly fail. One-third of the cancers affecting man are found where acidity is constant and high, as in the stomach. Cancer occurs but 2 times in the whole length of the alkaline small intestine to 98 times in the large bowel, in which again there is acidity. The same statement may be made concerning the development of cancer in the urinary bladder, cervix and mouth. A peculiarity also is that ulcer of the duodenum is three times as frequent as ulcer of the stomach, yet cancer of the duodenum is very rare. The mammary gland, uterus and prostate, subject to carcinoma, are tissues in which degeneration is a normal process and having but a limited period of functional activity. The danger of cancer is increased by all irritation or traumatism which demands a continued cell repair, and is in proportion to that demand. Ultimately exhaustion of cell control bodies occurs, modified by age limitations and chemical surroundings. C. H. Mayo (Can. Pract. and Rev., Nov., 1918).

The writer suggests that cancer cells represent a cellular revolt which ends in the death of both the cells themselves and the tissues in which they proliferate. Slight irritation maintained or a sudden shock is sufficient to cause this revolt only in pre-disposed tissues. Audrain (Progrès Méd., Feb. 22, 1919).

**Artificial Culture of Tissues and Cells.**—It is only in recent years that the study of growth of tissue on artificial media has opened a new direction for investigating cancer tissue production. The Imperial Cancer Research Fund in England, the Rockefeller Institute, the Institute at Buffalo, the Hutchinson Memorial, the Memorial Hospital in New York, the Crocker Memorial in New York, the Middlesex Hospital in England, and the Institute for Cancer Research in Berlin, as well as many others, have all been actively engaged in the

elucidation of the cancer problem, and most of their labor has been expended in study of the living cell and its reaction to changes in environment.

Carrel has found that tissue growth and reproduction may be carried on through many generations. Connective-tissue cells have been grown through successive generations for 13 years. It has been found necessary to renew the nutritional medium many times. It has also been found essential that a reticulum be present to act as a supporting structure. This may be a fibrous reticulum formed when the plasma coagulates, or may be an entirely foreign body, as a spider's web, silk thread, etc. It is also necessary to have present some activating substance, such as that contained in the juice expressed from embryonic tissues, before the growth activities of the tissue materialize. It is now thought that these substances present in embryonic extract act both as growth-stimulating (archusic) substances and as nutritive substances. The plasma or serum in which the tissue rests cannot be used as food because it contains proteins which cannot be broken down and used by the cells of the growing tissues.

The embryonic extract must be of the same type of tissue. Extracts of leucocytes may also be used. It has been found that leucocytes secrete substances which are analogous to embryonic extract in their stimulating quality; likewise, that the lymphocytes can live in media unsuitable for the fibroblasts and cell tissue growth, and that they can convert such a medium suitable for growth. It is necessary, too, that the proper  $pH$  be present. According to Lumsden,  $pH$  7.7 is the upper limit. Krontowski and Radzmowlka believe that the limit may be as low as  $pH$  3.4 (HCl sol.) or as high as  $pH$  10.28.

Single cells have never been cultured. The cells which have wandered deeply into

the media and have severed their connection with the tissue may grow for a time, but they ultimately die.

In artificial tissue growth it is necessary to have growth with metabolism. In the resting tissue of an adult organism there is only metabolism, without growth. There is in artificial growth of tissue no terminating mature stage where growth ceases; the growth goes on forever so long as the nutritive factors and stimulating substances are present. Thus, it has never been possible to develop the mature growth-terminating structures from ancestral cells, *i.e.*, bone and cartilage have never been developed artificially from connective tissue cells,—cells under artificial growth will not differentiate. The nutritive substances in embryonic tissue necessary for growth are called trophones.

It has been found that chicken sarcoma can be produced by inoculation under appropriate conditions of material from a chicken sarcoma which has been passed through a Berkefeld V filter. The size of these organisms, if they are organisms, must be under 0.4 micron. The microorganism *V. percolans* (diameter about 0.36) passes through the Berkefeld V filter while *V. cholera* (diam. 0.46) will not pass through. The average diameter of all three, *V.*, *N.* or *W.* types, is about 0.4. (Stuart Mudd).

It has been found that white cells can live and grow in a medium unsuitable for other cells, and that they convert an unsuitable medium either by specific decomposition or by the addition to the medium of certain secretory (or degenerative) products. Carrel holds that a similar process occurs in the organism itself, and that restitution of tissues occurs only if leucocytes are present. Lymphocytes are better than the polymorphonuclears as to growth and reproduction of a single cell. It has not been possible to keep tissues alive *in vitro* under conditions which exist in the organism, *i.e.*, metabolism without growth.

Another fact to be noted of tissue culture *in vitro* is that none of the cultured tissues grew to growth maturity with differentiation into other tissues. No connective tissue grew and differentiated, so that cultured tissue always remained of the same type; mesenchyme cells of the heart of the

chicken remained of the same fibroblastic type in cultures continued for years.

Adult differentiated cells in culture never revert back to the original embryonic type, but always retain the characteristics which they have developed during their period of development; a liver cell in culture does not revert to the original mesenchyme type, but always remains a liver cell.

When adult differentiated cells are grown, they produce secretory products of the same type as the original tissue; thus, Ebeling found that thyroid epithelium grown as long as five months in culture will form acini filled with a colloidal substance that is stained just as is the original tissue.

Burrows (Jour. of Cancer Research, June, 1925) believes that normal cells secrete a growth-stimulating substance that acts normally when the cells are separated from each other, but should the cells be crowded together, particularly if the blood supply is disturbed so that the growth stimulating intermediate substance is missing, excessive and irregular growth occurs, *i.e.*, malignancy. Burrows cites the fact that cellular growth in the embryo slows with the development of the blood vascular system. He cites, as an example of his idea, that skin wounds heal because the cells are massed together; as soon as the cells are separated and circulation develops, growth ceases. Any cellular mass of tissue having a reduced circulation may dominate over and eat up a less cellular mass no matter what may be the character of the cell in either of the two. Jorstad (*Ibid.*) states that a normal product of the cells is a substance called archusia which, when there is a concentration of the cells, causes a product called ergusia to be formed. This is absorbed by the fats and proteins, during which process they are drawn into the cells. A further concentration causes digestion of the fats and proteins, while a still higher

concentration of the cells causes a digestion of the cells themselves.

Again, Burrows (South. Med. Jour., xvii, 1925) finds that the most active development of tissues corresponds to the entire embryonic period of life up to the formation of the last uriniferous tubules and last glomerulus about 10 days after birth. The second period corresponds with the development of the organs to adult size; the third period is the period of arrestment in which cell reproduction is in equilibrium with cell destruction. When cells are transplanted, their activity of growth corresponds with the period at which they were obtained. Embryonic tissue is more active than adult tissue and early embryonic tissue is more active than late embryonic tissue. This explains why a fibrous sarcoma grows more rapidly than a cellular sarcoma and an adeno-carcinoma more rapidly than a cirrhotic carcinoma. A cancer cell is nothing else than an ordinary cell living under certain external conditions engendering augmented intensity of growth; it is not identical with an embryonic cell, but it grows like the latter; it grows actively and independently, owing to a strange organization.

Mitsuda and Chuma and Chlopin found that proliferation of the connective tissue and epithelium was most intense in cultures where epithelium and connective tissue had grown apart. Fischer (Zeit. f. Krebsf., xx, 342, 1923) found that tumor cells only retain their virulence as long as they are cultivated in tumor plasma. If they are not grown in tumor plasma they gradually revert to normal metazoic cells.

Frau Rhoda Erdmann (Zeit. f. Krebsf., xx, 322, 1924) finds that when she grows carcinoma tissue with its stroma for 14 days in tumor plasma and embryonic extracts,

the tumor cells finally dissolve the connective tissue cells. These tumor cells themselves become degenerated and disappear. The connective-tissue cells, however, disappear much earlier. The medium she uses is tumor plasma, 3; normal plasma, 6, and embryonic extract, 1 part. This renders the staining of the preparation for microscopic examination very difficult. The medium is prepared as follows: Rats are injected with pulverized embryonic liver or with extract of the pulverized embryonic liver or with grown rat liver on the day before the plasma is to be collected; on the next day the blood is collected and the plasma separated. To this medium is also added liver extract, forming a cloudy fluid.

If the growth is slow or bad Frau Erdmann uses 0.5 per cent. of rat embryonic extract, added to the culture medium. In observing the culture of carcinoma tissue, one should be careful of leucocytes which have also been transplanted, because they lose their granulation and then look like carcinoma cells. Carcinoma cells are defined by their very deeply colored nuclei and by their plasma, which is present as long as they are living and are perfectly healthy. When they begin to degenerate the plasma is very often changed and the nucleus deteriorates. The cancer cells disappear from the culture. Pure cultures of carcinoma cells which had been grown in normal plasma, after they had been cultured for a few weeks and then were transplanted, would not produce tumors. The same occurred with carcinoma cells which had been cultured in tumor plasma. Pure connective-tissue cells and carcinoma cells which have been cultured separately for a long time in normal plasma and then transplanted will produce no tumors. However, tumor and carcinoma cells which are in organic relationship and have been cultured for a short time in tumor plasma produce, upon implantation, tumors after a somewhat prolonged period. This observer regards cancer as a metabolic disease of the connective-tissue brought about through an unknown agent which causes an irritation or stimulation to the formation of the epithelial cells.

**The Cancer Cell.**—The cell is the central point of a system on which

are focused all the factors concerned in cancer production. This applies to plants as well as to animals, for Auler states that "trauma which in plants causes disturbance of the upward and outward flow of plant juices leads to the production of organic acids and the production of tumors in plants."

That free acids, especially the lower fatty acids and their  $\text{NH}_2$  derivatives, cause growths in plants has been the subject of experimentation by H. Auler. These acids are ferment products the result of deficient oxygen supply and are produced by the (plant) cells themselves.

F. Blumenthal and Paula Meyer produced papillary growths on the stalk of a turnip with lactic acid. In the growth from the *B. tumefaciens* are found many fatty acids—formic, acetic, and lactic acids. Petri produced growths in *Vitis* by injection of 0.2 per cent. sodium glycolate solution. Popoff produced growths in turnips by irritation with 8 per cent.  $\text{MgCl}_2$  + 12 per cent.  $\text{MgSO}_4$  or with 7 per cent.  $\text{MgCl}_2$  + 14 per cent.  $\text{MgSO}_4$  followed by washing with tap water.

Nabokich found multi-nucleated cells in anaërobic cultures. In crown gall are found many multi-nucleated giant cells. In this tumor, as soon as the larva dies, *i.e.*, the irritation ceases, the growth stops. Growths may also be produced by parasites on the potato (*Synchytrion endobioticum*). Cabbage hernia (*Plasmodiapheras brassicæ*) may likewise be produced by chemical agents (Blumenthal, Paula Meyer, Bitlman) and by X-ray (Hideo Kremori). There is but little difference in the character of the growth according to the causative factors. The growths always push

a layer of normal tissue before them. There are also many branched cells whose branches push out into the neighboring tissues, producing an infiltrating growth.

Auler (Zeit. f. Krebsf. xxii, 393, 1925) states that many organisms, viruses, etc., giving rise to new growths have a very intensive glycogen metabolism.

The cancer cell is probably a normal cell of the body, but has changed characteristics as far as metabolism, growth and reproduction are concerned. It grows faster in the serum of animals affected with cancer than it does in normal serum. Rhoda Erdmann concludes that cancer cells have greater vitality than normal cells from the fact that when cultured *in vitro* and reintroduced into the body they will survive, while under the same conditions normal cells will die. A further fact of importance is that in cultures in cancer serum, the cancer cell remains a cancer cell, but when transferred to normal serum it becomes a normal cell. It is possible that blood transfusion may be of some help in the treatment of cancer. In this work of Rhoda Erdmann cancer cells were for the first time transformed back to normal cells.

Epithelial cells in pure culture do not differentiate, but when connective tissue cells are added, differentiation sets in, so that squamous epithelium produces *Kratzen* (concentric corpuscles). Mammary epithelium produces acinous branching structures. Normal cells will live in fluid in which cancer is cultured. This fluid is poisonous to tumor cells, *i.e.*, the cancer cell produces an antibody to itself which is lethal to its own organism.

According to Turner (Practitioner,

July, 1923), cells, when they lose their function, do not necessarily die, but, if they have nourishment and the external stimulants of growth, continue to live and multiply. If central control, through the sympathetic, to the cells be cut off for one reason or another, a control factor is eliminated, whereupon the cells, no longer controlled by function, live and multiply independently.

**PATHOLOGY.**—The exact definition of what constitutes cancer is a matter of some difficulty, for the reason that no sharp dividing line exists between non-malignant and malignant new growths. Many tumors, particularly those of the *thyroid gland*, are *histologically adenomatous* and yet follow a *most malignant clinical course*. Gierke, from his study of animal tumors as well as of human new growths, concluded that no expression of opinion as to the degree of malignancy is possible from the histological structure. Apolant has shown definitely that *adenomata of mice* can pass into *carcinomata* and that *carcinomata* can again pass back into the *adenomatous* form of tumor.

*Mixed tumors of the parotid* also furnish illustrations of a form of neoplasm which histologically possesses the structure of a malignant new growth, but clinically amounts to very little more than a benign tumor; after complete local removal they never return, and after incomplete removal they may return locally, but do not form metastases.

The very interesting tumors known as *adamantine epitheliomata* also illustrate this fact. In these the histological structure shows every criterion of a malignant new growth, and yet clinically their course is benign. Almost the



same statement may be made of many epitheliomata of the skin. Their histological structure is of a most malignant character, and yet their growth may be very slow, and, while they may form metastases, still this occurrence is among the rarest of events.

Similar examples may be found in the many forms of *chondrosarcomata*; in fact, the gradation between simple chondroma and chondrosarcoma is an insensible one.

The growth of a carcinomatous tumor is, of course, in general different from a benign tumor or tumefaction due to bacteria; first, especially as to metastases. The cancer cells become transplanted in tissues and displace the tissue cells. The tissue cells take no part but are passive in the reaction. In the tumefactions due to micro-organisms, the tissue cells themselves have an active part and action; reaction takes place and an excessive localization of leucocytes occurs.

Cancer cells may produce the same secretion as the normal cells. Eiselberg found that thyroid cachexia occurred after excision of carcinoma of the thyroid. This disappeared in the development of metastases, upon the removal of which it again appeared. In relation to the above, it is of interest to know that Hansemann indicated that the functions of the cancer cells are: (1) Secretion; (2) geotropism, *i.e.*, the ability of certain layers to be supported and to grow in extension; (3) movement; (4) phagocytosis; (5) the ability to undergo certain changes, cornification, degeneration, etc. The tumor cells can produce changes and functional secretions similar to the mother cells; thus, liver carcinoma can produce bile. There is no principal difference between tumor and ordinary tis-

sue cells in a chemical or pathological way.

As has been mentioned, closely related to the failure of a sharp division line between benign and malignant new growths is the question of the transformation of one kind of tumor into another.

There is definite evidence that *metaplasia* in this sense occurs, but only to a limited degree. Certain *cystic tumors of the breast* have subsequently become carcinomatous, and quite a number of *polypoid tumors* of the rectum have been reported, upon which epithelioma has arisen at a later date. Whether the so-called *carcinomatous degeneration of a myomatous uterus* is a metaplasia of this kind is doubtful; in instances of this class what occurs may simply be a growth of carcinoma in the uterine mucous membrane overlying fibromyoma. A fairly large number of *cutaneous epitheliomata originating in congenital moles* have been observed. Volkman, out of 223 cases of cancer of the extremities, has reported 11 cases of cutaneous epithelioma beginning as congenital moles. Schafstein recorded that in a series of 989 carcinomata of the breast 23, or 2.3 per cent., developed from previous adenomata. Semon, out of 10,774 miscellaneous cancer cases, reports that 45 grew from benign tumors.

A consideration of these facts makes it clear that the metaplasia of one kind of tumor into another occurs only in rare instances, and then the transformation produces a closely related tumor. Indeed, one may fairly raise the question, in regard to the majority of cases cited as instances of the transformation of benign into malignant neoplasms, whether the malignant tumor does not actually arise "*de novo*," in the

manner suggested in the discussion of uterine fibroids.

The calcification of certain tumors, the formation of cartilage in others, and the changes in form and shape of the different varieties of epithelial cells can all be viewed in the light of various retrogressive changes; similar changes also occur in many other pathological processes. In neither case do they transcend the limit permitted by the biological possibilities of the cells in which such changes occur. Nevertheless, these possibilities are sufficient to render it impossible to draw a clear-cut line between malignant and benign tumors.

Characteristic of cancer tissue is growth and local extension. This occurs (1) by infiltration with destruction; (2) infiltration without destruction; (3) partly infiltrative and partly destructive. The infiltration of tissue into neighboring tissue is no definite sign of malignancy. The definite indication is the destruction of the cells of the neighboring tissue by the infiltrating growth.

In some instances, in chronic inflammatory processes, especially when associated with ulcers or fistula, the epithelium follows the newly-formed connective tissue and may infiltrate into the neighboring tissues. A malignant cell contains in itself the power of infiltrating and of destroying adjacent tissue. The infiltration is accomplished by the ameboid activity of the cancer cells. This activity, however, is also possessed by normal cells. The cancer cells must have some influence on the surrounding tissue cells, perhaps in the nature of a pathological ferment, so that they are destroyed, thus permitting the cancer growth.

The dissolving property of the cells

is shown by the ability of the cancer cells to break through the walls of blood and lymph vessels, in the lumen of which they continue to grow so that large branches are involved. The walls are enormously stretched. A thyroid tumor can grow in the vessels until it reaches the superior vena cava and the right ventricle, and likewise an adrenal growth can progress until the inferior cava is reached. This character of growth has also been observed in the lymph vessels (thoracic duct). Occasionally the entire lymphatic system of an organ may be involved (lungs). The ducts of an organ may also act as guides for cancer growth, as in mammary cancer; in some instances the cancer extends by filling up the normal ducts. The gall ducts and urinary small canals are likewise involved.

**Malignant Tumor Definition.**—A malignant neoplasm then, may be defined as one whose cells exhibit a *progressive tendency to invade the neighboring tissues*, either singly or in masses. In such a neoplasm there is *no true encapsulation*.

A *benign* tumor, on the other hand, is *encapsulated*, and, while increasing in size as a whole, *encroaches upon*, rather than invades, the neighboring tissues. Such a criterion as this always makes it possible to place certain of the borderline growths in a correct classification; on the one hand, neoplasms which, although benign, still, on account of their size and sometimes even from their rapidity of growth, are capable of destroying life, and, on the other hand, growths which, although malignant, may run a relatively harmless course, and unless removed with special thoroughness, always recur and are capable of hopelessly destroying the neighboring tissues.

Malignancy is indicated by the following signs: (1) Continued capacity of the cells for rapid growth. The extent of this varies; in some tumors, the growth may be slow, while in others it may be very rapid, and in some instances a spontaneous recession may occur. At times rapidity of growth may alternate with retardation.

(2) Infiltrative and destructive growth into surrounding tissues. This is not particular to malignant tumors alone, since *normal* chorion epithelium grows into the uterine decidua. However, these are foreign cells, as they originate from the fetus. Destruction by cells derived from the body itself is present in malignant tumors only. It differs from inflammation in that, in this instance, the cells are destroyed in resisting foreign invaders, bacteria, etc.

(3) Tendency to metastasis formation. This is not absolutely necessary, however, to indicate that the tumor is malignant, for it may be absent in a very malignant tumor. Normally the blood cells may pass out of the blood-vessels and multiply. This is well exemplified in abnormal processes such as inflammation, in which there is here a certain similarity to metastases in tumor formations. It has been held as possible to implant ovarian tissue in the laparotomy wound during an operation and have a cancer develop. Borst also mentions the tumors in bone which have the structure of the adrenal and the thyroid. These may be due to metastasis with malignant change of normal cells which have gained entrance to the blood circulatory system. It may also explain the presence of chorio-epithelioma from the entrance into the circulation of normal chorio-epithelium.

According to Wolbach (Amer. Jour. of Roentg., Feb., 1925), the acquisition

of malignant properties is not a sudden one but takes place in the course of years. Reactions on the epidermis are secondary to reactions in the corium.

**Classification.**—Malignant neoplasms may be divided into those of mesoblastic origin and those of epiblastic origin.

I. The *mesoblastic* tumors are those which consist of an unrestrained reproduction of a mesoblastic type of cell. They may be further subdivided into:

a. Sarcoma; an unrestrained reproduction of a connective-tissue type of cell.

b. Lymphosarcoma; an unrestrained reproduction of a lymphoid type of cell.

c. Endothelioma; an unrestrained reproduction of an endothelial type of cell.

d. Glioma; an unrestrained reproduction of the glia type of cell.

e. Melanoma; an unrestrained reproduction of the chromatophore cells.

II. Malignant tumors of *epiblastic* origin may be subdivided as follows:—

a. Malignant adenoma; a tumor preserving adenomatous characters, but being to a greater or less degree an unrestrained proliferation of a glandular type of cell.

b. Carcinoma; an unrestrained reproduction of a glandular type of cell.

c. Epithelioma; an unrestrained reproduction of an epithelial type of cell.

A discussion of cancer must include these different kinds of tumors, although the chief interest centers around sarcoma, epithelioma, and carcinoma. All three of these are of frequent occurrence, and together are responsible for about 5 per cent. of the deaths over 35 or 40 years of age.

About 6 per cent. of all patients dying in Bellevue Hospital and coming to autopsy are subjects of malignant

disease. Of 298 malignant tumors observed *post mortem* at this hospital, 220, or 74 per cent., were attended by metastases. The lymph nodes, liver, pleura and lungs, bones, and adrenals were the organs most commonly metastasized, and they were involved in the order named. Epithelial tumors predominated over those of connective-tissue origin in the proportion of 8 to 1. The lymph nodes, liver, lungs, pleura, and bone marrow give rise to malignant growths only rarely, but metastasis to these organs is common, while the stomach, breast, pancreas, prostate, etc., frequently give rise to malignant tumors, but are themselves seldom metastasized. D. Symmers (Amer. Jour. Med. Sci., cliv, 225, 1917).

**Malignant Tumors of Mesoblastic Origin.**—The *sarcomata* are composed of cells, intercellular substance, and vessels. The cells vary much in size, shape, and number in different tumors. The most typical form is spindle shaped, each end tapering off into a fiber of considerable length. In many tumors these cells are arranged close together in bundles, and are of small size; such a tumor is less malignant. In others the spindle cells are larger and relatively not so long, giving them a plumper appearance and a larger nucleus in the center; these tumors are more malignant. Other sarcomatous tumors are composed of cells which are almost round, or more or less cuboidal and polygonal, owing to pressure of contiguous cells. These tumors are still much more malignant; their cells vary much in size. In the more rapidly growing tumors *nuclear division may outstrip the division of the cells*, thus giving rise to very large cells with many nuclei (*giant-cell sarcoma*). In other tumors karyokinetic division may proceed so rapidly that the normal orderly sequence of changes is not pre-

served. This results in many *irregular nuclear figures* and in *unequal distribution of the chromatin contents of the daughter-cells*. In the more malignant and rapidly growing tumors the *intercellular substance is scanty in amount*, while in the slower growing forms it is more abundant, and this is particularly true in regard to the spindle-cell sarcomata. The character of the intercellular substance varies greatly. In some forms it may be *collagenous and fibrillar*; in the latter tumors the fibers form a part of the intercellular substance.

In other sarcomata the intercellular substance is largely composed of *mucinogenous substance*; when this is present in large amounts such a tumor is named *myxosarcoma*. In the same manner the *chondrosarcomata* and the *osteosarcomata* are differentiated from each other by the character of the intercellular substance. In still other tumors there may be a combination of an unusual proliferation of the blood-vessels with a true sarcomatous development of the connective-tissue supporting framework. When this is the case we have a mixed tumor formation, and the condition is named *angiosarcoma*.

Sarcomata may occur in any portion of the body. Their favorite sites are the long bones of the extremities or their periosteum; they also frequently occur in the subcutaneous tissue. They are more rare in connection with the internal organs. The kidney and uterus are perhaps more frequently attacked than other organs; they are not uncommon in the testicles and ovaries. They are less frequent in the breast, and occur still more seldom in the other organs.

Deserving of special mention are the *myeloid sarcomata* of the long bones.

Histologically these present groups of giant cells separated by a very characteristic spindle cell. The giant cells are not always evenly distributed throughout the tumor, but tend to be collected together in groups; they are very large, often containing as many as 50 to 100 nuclei. Their appearance suggests normal osteoblasts. The formation of new bone in these tumors approximates also the physiological method. An osteoid substance is deposited and along this are arranged the spindle cells, in such a manner that one can attribute to these cells true osteoblastic functions. This approach to the true physiological process is in direct unison with the benign nature of these tumors. Their favorite sites are the gums (malignant *epulis*) and the marrow of the long bones, especially of the extremities. A very frequent location is the lower end of the femur. As the tumor grows it presses the shell of bone surrounding it in a peripheral direction, until finally this becomes so thin that it will creminate on pressure like an eggshell.

In certain vascular tumors an actual pulsation occurs, producing the so-called bony aneurisms. In bones which are the seat of these tumors, spontaneous fractures are most liable to occur.

The *chondrosarcomata* are rarer; when they occur in connection with the internal organs they are often classified as mixed tumors of these organs. Finally there may occur tumors containing both bone and cartilage. Although these usually originate from the periosteum, they may also occur in portions of the body in which this membrane is not present, as the breast or bladder.

Sarcomata increase in size by both invading and pushing aside the surrounding tissue. No tissue is able to resist their progress; the skin ulcerates

over them, and bone atrophies and necroses before them. Sooner or later they invade either the blood-vessels or a lymphatic stream in their path, and small particles of tumor-tissue are swept away, to lodge in distant locations. These then grow as metastases and always reproduce the primary tumor in its typical structure in the locations where they lodge. Sarcomata do not often invade the lymphatics, and when they do they rarely pass the glands to which the lymphatic stream leads which drains the region of the primary tumor. This method of metastasizing occurs most often with the softer, round-cell variety of sarcoma; *the usual manner of metastasis in sarcoma is through the blood-vessels. The wall of the vessel is entered, and a small portion of the tumor is carried away, which lodges in the first small-sized vessel or capillary which it meets and through which it is unable to pass.* Naturally, therefore, the most frequent location for metastases is the lungs, or the small divisions of the portal system in the liver. For the same reason the terminal vessels of the brain and kidney are frequent stopping places of these metastatic emboli. No portion in the body, however, is exempt, and after death from sarcoma it is not unusual to find many organs in the body affected.

The degree with which the metastases reproduce the primary tumor is of interest. In the osteochondrosarcomata the metastases also contain bone and cartilage, so that the various cells of the tumors retain the capability of forming bone, cartilage, and fibrocellular tissue. *In actively proliferating tumors the metastases often exaggerate the more atypical characters of the neoplasm; the cells are less well formed,*

or the *giant cells are more numerous and irregular in appearance.*

A very special and important form of sarcoma, and one which is associated in a peculiar manner with the skin, is *melanoma*. It forms a group of tumors differentiated from other neoplasms by very definite characteristics.

Melanotic tumors may originate in the choroid coat of the eye or in the skin of any portion of the body; a favorite starting point is the outer surface of the lower leg, and the skin in the region of the umbilicus. The primary tumor may exist for years, indeed, throughout life, without showing any proliferative tendencies; then suddenly, without apparent occasion, or perhaps after an attempted removal, it will begin to grow and almost immediately take upon itself most malignant qualities. These tumors are of very rapid growth, and form very extensive and early metastases, and there is scarcely any neoplasm more malignant. It is not unusual also for the same anomaly to exhibit itself in the metastases which may have remained quiescent for years, and then suddenly grow at a very rapid rate. When cases in which the metastases exhibit such a course occur after the excision of the primary tumor, the clinical history is very unique. The patient may remain well for years, indeed, so long that he or she has entirely forgotten about the removal of the small, discolored wart two, three, or even five years previously. A rapidly growing tumor then develops within the brain or in some other internal organ, and the patient quickly succumbs.

It is from this fact that the error has arisen of supposing that it is a dangerous practice to remove pigmented warts. *Often these are not removed until they show some evidence of growth; then*

*metastases have occurred and the patient will succumb from general melanoma in a relatively short time.* The common interpretation of such a course of events is that the excision has been responsible for exciting the otherwise harmless mole into a virulently active growth. As a matter of fact the author feels convinced that in these cases metastases had already taken place at the time of excision, and not as a result of it. In this class of cases, there has seldom been any recurrence at the site of the original tumor, if the patient is fortunate enough to have had a proper excision, and not such incomplete and stimulating forms of treatment as curettage or caustic applications. *When recurrence takes place only in distant portions of the body, and not in the site of the primary growth, it must be assumed that this latter has been completely removed, and this, therefore, is an argument for the early removal of all pigmented growths, without waiting until they have begun to develop a malignant character.*

The pathology of these tumors is as characteristic as their clinical history. They are composed of cells presenting a great variety of forms; often they are definitely epithelioid in shape; at other times fusiform, with a number of branching processes; again they are definitely spindle-shaped, each end being drawn out into a long, slender process. The typical cell of these tumors contains pigment; but many cells, even from darkly colored lesions, are not pigmented, and some typical melanomata contain no pigment. Another peculiarity is that many of the metastases arising from deep-colored growths may be pigment free.

The connection of these tumors with congenital nevi raises an interesting

question. Are they in any way related to nevi? The author believes that the term nevus is used much too loosely. Two rather definite forms of growths are included under this name. We have, first, vascular nevi, in which the tumor is composed of endothelial cells, forming, in a more or less perfect manner, walls of small vessels, and, second, we have the congenital, discolored growths, known as pigmented nevi, in which no vessel walls are found, but only cells which on superficial inspection show many similarities to those of vascular nevi. To apply the name nevi to these latter tumors is misleading; they form a definite entity by themselves. Many of them may be entirely unpigmented; in many the cells are more or less cuboidal in shape. It is particularly in connection with this latter class that melanoma arises, and study and comparison of these various growths with themselves, and with melanoma, suggest that these congenital neoplasms are really cell-complexes which have been set aside during the process of development, and, in fact, represent the early stages of true melanoma.

The interesting question next suggests itself, whether we shall consider these melanomata as epithelial tumors or as of connective-tissue origin. Their close relation to epithelial structure, their pigment-forming property, the peculiar shape of many of their cells, particularly in some of the early nevoid forms, suggest to many observers that they must be of epithelial origin. On the other hand, the fact that no direct connection exists between them and the epidermis and the tendency to a fusiform shape of their cells in their most typical form (demonstrated so clearly by Ribbert in teased preparations from choroidal growths) make the term

melanotic sarcoma correct for other observers. Ribbert, who has done the most work on these growths, believes them to be of connective-tissue origin, and that they represent a special form of pigment-forming connective-tissue cell, to which he applies the name chromatophore. Nevertheless, there has been an increasing tendency of late to regard them as epithelial, and to employ the term melanocarcinoma.

A form of sarcoma which is of very great interest both clinically and pathologically is *lymphosarcoma*. The units composing this tumor are the round lymphoid cells of the lymphatic glands. With these, larger cells are also present, possessing a relatively greater amount of protoplasm, and resembling the cells of the follicles of the gland. The endothelial elements of the gland also undergo proliferation, and the results of this may at times form considerable portions of the tumor. In other growths, especially those with large amounts of lymphoid cells, the supporting connective tissue and endothelial elements may be present in only small amounts. The changes in the endothelial structures in no way differ from similar changes present in inflammatory processes. In many of them several nuclei may be present, so that giant cells may be of frequent occurrence. Another kind of cell often found in these tumors is the eosinophile cell; it is not always present, but, when it is, it is of diagnostic importance. A fine reticulum supports all these elements, and this varies in amount in an inverse ratio to the other components. It may even to a large extent replace the true elements, and in such cases gives rise to firm, hard tumors.

The locations of preference for lymphosarcomata are the lymph-glands of

the neck, axilla, and anterior mediastinum; in the latter region the thymus may form the starting point of the growth. Less frequently they may arise from the palate, tonsils, and lymphatics of the intestinal canal, and still more rarely from the spleen, liver, lungs, or even mamma. The tumors are essentially malignant growths, and their metastases invade every organ.

Another change which is peculiarly associated with these tumors is the collection of lymphocytes within the blood. It is natural to suppose that the tumor elements are easily swept into the circulation and there collect, producing a relative lymphocytosis. Ribbert even concludes that not only is pseudoleukemia a lymphosarcoma, but also leukemia, and that the latter is simply a later stage of the disorder.

**Malignant Tumors of Epiblastic Origin.**—Under this head must be described a number of tumors whose pathology approaches closely that of simple adenoma, and whose growth is mainly expansive, and, yet, the more rapidly growing of which possess invading qualities and form extensive metastases.

Neoplasms of epithelial origin deserve a separate classification from true carcinomata, for the reason that there is every gradation between their simple benign forms and the malignant varieties; the former are slow-growing, well-localized, and encapsulated adenomata.

The pathology, however, is essentially the same as in the more malignant, progressive, and metastasizing forms, and every intermediate step may be observed between them. They illustrate well the point mentioned that no sharp line of division exists between benign and malignant tumors. These tumors

include cylindroma, which occurs chiefly in the oral cavity, in the palate, on the floor of the mouth, in the region of the salivary glands, in the orbit, or in the accessory nasal sinuses, rarely elsewhere. They are characterized by anastomosing columns of epithelial cells, of varying thickness and configuration. Between these, or within tubes formed by them, dependent partly upon the collection of the secretions of the cells, and partly upon a hyaline degeneration of the stroma, is a clear, more or less homogeneous material, from the tube-like character of which the tumor obtains its name. These tumors are essentially benign; they rarely recur after removal and more rarely still from metastases.

**Mixed Malignant Tumors.**—For the sake of completeness, mention will be made of the *mixed tumors of the salivary glands*, especially of the parotid; these should never be classed as carcinomatous. They do not form metastases, and when properly removed do not recur. They are composed of columns of cells, sometimes solid, sometimes inclosing spaces or concentric pearls of flattened cells. Such definitely stamp the cellular portions of the tumor as epithelial and not endothelial. The arrangement of these cells is very like that in cylindroma, the only difference being that there is not the extensive amount of the same type of degenerative changes and secretory collection as in the latter. The peculiar feature of the mixed tumors of the salivary glands consists in the great variety of different kinds of mesoblastic tissue between the epithelial portions of the tumors. The epithelial columns may be separated by mucous tissue, by ordinary connective-tissue stroma, by fat, by cartilage, and even by bone. The



locality of the salivary glands, particularly the parotid, is such that it is an easy matter to conceive how developmental abnormalities could cause the deposition of all these varieties of mesoblastic tissue among the lobules. These tumors become malignant even more rarely than the cylindroma, but at times their epithelial portions may burst the capsule and develop into real carcinoma. They find, therefore, a place in a discussion of malignant growths.

The *adenomata* of the breast, prostate, and kidney may be omitted in this discussion, but adenomata of the adrenal and liver are frequently malignant, and, therefore, deserve special mention. Of particular interest are the adrenal adenomata, otherwise known as *hypernephromata*; the interest centers around the very wide distribution of embryonal complexes of adrenal tissue. Small masses of this tissue occur widely distributed throughout the body; they resemble in every way the adrenal, with the exception that the tubules, when definitely present, are not arranged in an orderly direction, but irregularly anastomose and wind around. These complexes of cells are most frequent in the adrenal and in the tissue about it, or in the kidney. They are also encountered in the broad ligament, in the ependyma, on the under surface of the liver, and in the lesser omentum; also in the ovary and solar plexus. They form a strong argument for the development of tumors from embryonal complexes. When such tumors acquire malignant characters they often attain a very large size, even eight to nine inches in diameter. These tumors often show extensive necrosis in their centers, although they are very vascular and interstitial

hemorrhages are frequent. They are dangerous, both from their size and the frequency with which they metastasize. Metastases occur oftenest in the liver and lymph-glands, but also in the brain and lungs; the metastases result from the breaking of the capsule of the tumor and the invasion of the surrounding vessels and lymphatics (see ADRENALS, DISEASES OF, Vol. i).

Of similar significance are the *adenomata of the liver*. These most frequently occur with cirrhosis of the liver, and originate in multiple locations in that organ. Usually they remain of small size, undoubtedly representing small, regenerated areas; at other times, however, they take on a more extensive growth, and form tumors of the size of a walnut or apple. Not infrequently others become still larger and develop into definitely malignant growths, which then invade the vessels, especially the portal vein or the inferior vena cava, and thus become transplanted to other regions of the body, heart, lungs, bones, and lymph-glands.

The histology of these small tumors closely agrees with that of normal liver-cells; at times solid columns of cells are found; at other times the chains of cells surround lumina in the interior of which are cell detritus and gall-stained coagula. The metastases are often functional; many of them never develop, but frequently retrogress and perish. Ribbert assumes that these tumors grow from the liver-cells.

Similar adenomata grow from the *thyroid*; they resemble the thyroid parenchyma, but are easily distinguishable from it, and form metastases which show a predilection for the extremities of the long bones. Both the metastases and the original tumor are slow-growing and run a very benign course.

The consideration of these adenomata finds a proper place in the discussion of cancer, because those which we have described also occur in forms which are malignant. In the main, however, their growth is slow and expansive, and always so in their early stage. It is this feature of expansive growth that distinguishes them from true cancer. In true carcinoma or epithelioma the increase in size is, from the very start, dependent upon an infiltration of the surrounding tissue by new cells. Yet, after all has been said, the difference between these and the adenomata is only one of degree. Many of the carcinomatous growths must be termed adenocarcinoma, and, as was mentioned above, there is no sharp line between the two types. The writer desires to lay special emphasis upon this fact, as it establishes a closer relation between the normal tissue and carcinomatous tumors.

Carcinoma may occur wherever epithelial tissue is present. The essential element is the invasion of the neighboring tissues by groups of cells which present a greater or less deviation in their appearances from the normal cell. The different forms of these growths depend upon the different relation of these cells to each other and to the connective-tissue stroma, and also to the amount and character of this stroma. In general, the cells of carcinoma simulate the epithelium of the tissue or gland in which they arise. It may thus be adenomatous, or alveolar, or acinous, and at times the epithelial elements are so excessively developed that the tumor seems to be practically solid with cells. Such growths occur in any glandular organ, but particularly in the breast, gall-bladder, intestines, and lungs

In other tumors the glandular ele-

ments form anastomotic columns of cells, separated by a greater or less amount of stroma. In some slow-growing tumors, particularly of the breast, the cellular elements may also be few in number and separated by much well-organized fibrous tissue. Tumors of this kind are called *scirrhous carcinomata*.

In some tumors a single layer of cuboidal or cylindrical cells is found as a lining of glandular-like spaces. Cylindrical adenocarcinomata of this variety usually occur in the hollow organs, particularly the stomach, colon, or rectum; they also occur in the uterus, gall-bladder, pancreas, lung, prostate, and mamma. Other tumors show a papillary form of growth, with long, slender processes lined with a single layer of cylindrical cells. These occur especially in the bladder or uterus; they have also been described in the digestive tract. Many carcinomata secrete large quantities of mucus; this is especially true of the cylindrical-celled growths. The mucus collects in the interstices between the epithelial portions, producing the macroscopic appearance of a jelly-like substance; such conditions are generally termed mucinogenous degenerations. The analogous colloidal degeneration also occurs, but it is rare.

Case of *Krompecher's basal cell carcinoma* in a man of 56 years. The condition is peculiar in that the proliferation of the tumor cells takes place in a downward direction and results in the formation of flask- or club-shaped structures resembling glands. It starts from the deep-lying epithelial layers. As illustrated in the writer's case, the tumor was covered with normal epidermis. It was in the patient's external ear. Siedlecka (*Polska gaz. lek.*, June 11, 1922).

*Epithelioma of the skin* follows two main types of growth: the spinous or

*squamous-cell epithelioma*, and the *basilar-cell epithelioma*.

The cells of the squamous type resemble those of the *prickle cells* of the stratum Malpighii; they are large, connected to adjacent cells by spines, and tend to invade the surrounding connective tissue in large groups. Frequently they are concentrically grouped; by virtue of this and the continued proliferation, concentric masses of flattened cells result, forming the so-called "pearls." This *spinous* type is the most malignant form of epithelioma of the skin.

**Primary Tumors and Multiple Tumors.**—It is very difficult, in many cases, to define whether multiple tumors are metastases or new tumor formations. Billroth believed that multiple tumors should be defined as primary in origin only provided they are of different cell-types, *e.g.*, one of the skin and the other of the gastrointestinal tract, or tumors in different parts of the same organ, *e.g.*, a tumor of the cervix uteri and a tumor of the fundus. The first of these would show a flat epithelium and the second, a cylindrical epithelium. It should also be a test that each of these types of epithelium will produce metastases characteristic of the mother tumor.

Obviously, if carcinoma and sarcoma occur in the same person, they must be two primary tumors of different origin. In many cases it is difficult to determine whether the tumor is a metastasis or is a new formation from the fact that the histogenetic derivation of a tumor is very hard to define; much depends upon the judgment of the observer. There are different types of irritation primary carcinoma. We know that in animals, tar and paraffin can produce multiple carcinoma; also that in the scars of

lupus, cancer can occur; also, that multiple carcinoma can occur from the Roentgen ray; also, that there is multiple carcinoma present in polyposis of the gastrointestinal tract or in papilloma of the kidney pelvis or of the urinary bladder. We, likewise, find primary multiple tumors in cases of xeroderma pigmentosum.

Benign tumors are frequently multiple, *e.g.*, neurofibroma, chondroma, different types of exostoses, etc. Sternberg believed that in those who have multiple tumors there is a constitutional factor, and he spoke of tumor races. There may possibly be a special disposition of a person to such tumor formation.

**Metastases.**—In all forms of malignant tumors of epiblastic origin the formation of secondary growths at a distance from the tumor is of frequent occurrence, though the various varieties of tumors differ in the rapidity and frequency with which such secondary growths form and the sites in which they first locate.

In considering the origin of metastasis, one should discuss (1) whether metastasis is only associated with the nature of the tumor; (2) whether there is some general fact in the organism or whether there is a local disposition. Certain tumors, chiefly carcinoma, spread through the lymph pathways or involve the regional lymph glands which act as a filter. There are tumors which spread especially through the blood pathways, and with these, metastases occur in the places where are located the first capillaries through which blood going from the primary tumor must pass. It has been observed in these regional lymph-glands that a thickening of the walls of the lymph-vessels occurs, with narrowing and

partial obliteration of the lumen, hardening, and also contraction or atrophy of the glands. All of this may so reduce the protective powers as to make of the structure a good place for cancer tissue to lodge and grow. When the forward pathway is obliterated, the cancer frequently spreads backwards against the lymph stream. When there is total obliteration of the lymph pathway, the tumor cells cannot get through. It has been found, however, that tumor cells have the power to make themselves hard so that they may pass through and produce secondary growths beyond the barrier.

Metastases, aside from being the result of propagation through the blood and lymph pathways, may also arise by conduction over mucous or peritoneal surfaces, with location and implantation at distant areas. This process results in what are known as *contact metastases*, *inoculation metastases* and *impression metastases*. Rizzi reports a case of cancer in the upper part of the urethra which extended in a band 2 mm. wide superficially along the urethra to a large plaque in the anterior third of the urethra, from which a small band extended to a large tumor in the fossa navicularis, as far as the urethral orifice. Examination indicated that the extension had not occurred by lymphatic channels.

Scattering of the tumor elements may occur in ovarian papilloma (cystoma), so that multiple implantations take place. Contact implantation is illustrated by the occurrence of carcinoma on the opposite lip of the cervix when it is present on one lip. Implantation metastases are represented by abdominal wall cancer in the scar of the abdominal incision after operation for abdominal cancer. This may occur after a number of

years. Albert reported a case of generalized melanosarcomatosis occurring twenty-four years after the extirpation of a melanosarcoma of the choroid.

The occurrence of metastases years after a primary tumor has been removed may be explained by (1) increase during the interval of the capacity of the cell for growth; (2) decrease of the resisting power of the tissue (the immunizing protective substances may have in the course of years lost their activity). A tumor which has a relatively slow growth usually recurs relatively late. This may be explained by the intensity of the tissue resistance being gradually overcome.

Metastases are frequently much larger than the primary tumor; sometimes the primary tumor is so small that it is difficult to find. The metastases have the same form and structure as the primary tumor; as a rule, however, anaplasia is greater, so that at times it is difficult to define the relationship between the primary and the secondary tumor. Indeed, metastases often have characteristics which are missing in the primary tumor; thus, metastases in the bony system from prostatic carcinoma have the ability to stimulate bone formation and thus produce a sclerosis of skeletal tissue.

As has been indicated, sarcomatous metastases usually occur by the bloodstream. In carcinoma and epithelioma the cells, at first, almost always are swept away in the lymph-channels. Why it is that the metastases of these two forms of malignant new growths invade the body by means of different paths is not thoroughly understood. It may be due to the fact that a connective-tissue cell more readily forms a part of a vessel-wall than does a carcinoma cell. At any rate carcinoma and epithelioma

spread through the lymphatics. The cells of these tumors accomplish this not only by means of the direct extension of growth, but also by ameboid movement of individual cells (Ribbert, "Das Carcinom des Menschen"). In sections of these tumors their cells are seen filling the crevices of the stroma and lymphatic spaces.

By the vessels of the latter the cells are conveyed to the regional glands which, for a time at least, form a barrier to further extension of the growth. The efficiency of this barrier is best appreciated in squamous-cell epithelioma, which form of cancer never invades the general body beyond the first set of lymphatic glands.

The importance of metastases and the frequency of their occurrence with various tumors can be appreciated by the following table taken from Redlich's article, which shows the frequency with which cancer of various organs metastasize at the time of death:—

	No. of cases.	Cases dying with metastases.	Redlich's percentages.
Breast .....	26	26	100.0
Pancreas .....	8	8	100.0
Lung .....	30	29	96.6
Gall-passages .....	32	30	93.7
Kidney .....	8	7	87.5
Ovaries, vagina, vulva .....	15	13	86.7
Stomach .....	156	131	84.0
Uterus .....	34	27	79.5
Esophagus .....	52	39	75.0
Pharynx .....	11	8	72.7
Large gut .....	20	14	70.0
Rectum .....	23	16	69.6

In quite a number of instances metastases have involved organs without having attacked the lymph-glands. The frequency of such an anomaly with cancer of the various organs among the cases reported by Redlich is indicated in the following table:—

Stomach .....	17 times
Gall-passages .....	10 "
Large gut .....	4 "
Esophagus, lungs, uterus, breast, kidney .....	3 "
Ovaries, pancreas, rectum .....	2 "

The following tables show the percentages of cases of carcinoma of the various organs which had formed, at the time of death, metastases in the lymph-glands, on the one hand, and in the organs of the body, on the other hand:—

PERCENTAGES OF CARCINOMA OF THE VARIOUS ORGANS FORMING METASTASES IN THE LYMPHATIC GLANDS.

	Redlich's cases.	Feidchenfeld's cases.
Breast .....	88.5	92.0
Lung .....	86.6	71.4
Pancreas .....	75.0	61.5
Pharynx .....	72.7	
Stomach .....	72.4	70.3
Uterus and vagina .....	70.6	59.5
Esophagus .....	67.3	73.2
Gall-passages .....	62.5	73.1
Rectum .....	60.8	50.0
Large gut .....	50.0	40.0
Kidney .....	50.0	

PERCENTAGES OF CARCINOMA OF THE VARIOUS ORGANS FORMING METASTASES IN OTHER ORGANS.

	Redlich's cases.	Feidchenfeld's cases.
Pancreas .....	100.0	69.2
Breast .....	92.3	88.0
Kidney .....	87.5	
Gall-passages .....	81.3	84.6
Lung .....	66.6	52.4
Stomach .....	65.3	54.1
Vulva .....	46.6	
Vulvovagina .....	35.3	28.2
Rectum .....	31.8	50.0
Pharynx .....	27.3	

The second variety of epithelioma of the skin, the basilar type, reproduces cells which strongly resemble the cells of the basilar layer. Many forms of this tumor occur, and various sub-



Carcinoma of the Uterus. (*Küst.*)



divisions have been suggested, depending upon the arrangement of these cells. They have been divided into adenomatous, acinous, or cystic groups. In general, however, they all present the same essential characteristics, and the author sees no reason for subdivision of this class.

The early stages of these tumors consist of simple projections of thickenings of the basilar membrane into the corium. The invasion of the corium by these cells steadily increases, with the production of many different appearances, which may all be described by stating that the various groups of cells within the corium are of larger or smaller size, and are connected with anastomotic columns of varying thickness and length. When the adenomatous character is more marked, cystic degeneration is frequent. From the occurrence of these cysts the name *adenoma sebaceum cystoides* has originated. The tumors of the basilar type are all of a relatively benign nature; they are slow of growth, and, with rare exceptions, do not metastasize. Frequently the tumor processes are of great length, and in all of them the epithelial elements are very abundant. The absence of lymphatic metastases in mice is a striking feature when compared with corresponding groups in man (Narat, Maud Slye).

**Leukemia and Cancer.**—Weill has reported 8 cases of leukemia in persons who had been subjected to the X-ray or radium. One case occurred 4 years after deep therapy. No special type of the anemia was observed. Since leukemia is often (at least at first) favorably influenced by the X-ray, it has in this respect a close resemblance to cancer, and many have considered leukemia as a "cancer of the blood."

**Chemistry of Cancer.**—The chemistry of cancer at the present time is in a

very unsettled state. As Beebe states, "the chemical study of tumors is in its infancy. We have scarcely proceeded far enough to know where the medical problems are, nor have methods now available been perfected to such an extent as to enable a decisive experiment to be made." "No phase of metabolism," says this investigator, "has been described in cancer which does not have a counterpart in non-cancerous conditions. This applies to such questions as the nutritive relations between the cancer cells and the normal body tissue, to the nitrogenous balance, retention or elimination of sodium chloride, excretion of acetone, the relation of ammonia excretion, and to a possible acidosis. Diet doubtless forms an important part in the growth of cancer, possibly even in the origin of the disease." This view is confirmed by clinical experience and by work upon experimental cancer.

The question of the existence of specific cancer poisons is an important one. Evidence exists that such toxic substances exist, but no proof that they are effective in causing cancerous cachexia.

In nearly all cases of cancer and sarcoma examined the author found alkalinity of the serum greater than that of serum of normal individuals. M. L. Menten (Jour. Cancer Research, ii, 179, 1917).

Hydrogen ion concentration of older tumor tissue is usually less than that of healthy tissue. E. F. Smith and A. J. Quirk (Jour. of Cancer Research, viii, 537, 1924).

According to T. Lumsden (Lancet, July 12, 1924) the upper limit of serum in which tissue culture took place in his experiments was pH 7.7. In a unit of time, tumor tissue produces of lactic acid, 100 times as much as the blood; 200 times as much as does frog's mus-



cle resting, and 8 times as much as frog's muscle working to the limit of its efficiency. Tumor tissue acts like yeast; it *splits glucose* into lactic acid in the absence of oxygen as  $C_6H_{12}O_6 = 2C_3H_6O_3$ ; or, in the presence of oxygen, it acts by splitting glucose and oxidizing it as  $C_6H_{12}O_6 + 6O = C_3H_6O_3 + CO_2 + H_2O$ . Rat cancer produces 30 molecules of lactic acid for every molecule of oxygen respired.

Similarly, Warburg (Jour. of Cancer Res., ix, 148, 1925) states that human carcinoma possesses strong glycolytic activities and produces an average of 16 per cent. of its weight of lactic acid per hour. In tumors the respiration is too small to bring about the disappearance of the glycolysis products, while in normal tissues the respiration is sufficient for this. Aërobic glycolysis is practically *nil*. As Warburg says: "No growth without glycolysis, conversely no glycolysis without growth." In malignant tumors there is an oxygen deficiency: "Oxygen deficiency results in the death of all cells which do not glycolyze."

Surviving sections of rat carcinoma formed at least 70 times as much lactic acid from sugar as other rat tissues. The tumor can thus decompose its own weight of sugar in 13 hours and form 7.5 per cent. of its weight of lactic acid every hour. This process is inhibited by narcotics, but not by absence of oxygen. O. Warburg and S. Minami (Klin. Woch., Apr. 23, 1923).

*Lactic acid* found in the urine of most cancer cases as well as of cancerous mice after intravenous injection of glucose solution. K. Glaessner (Wien. klin. Woch., Apr. 10, 1924).

When cancer develops in a case of diabetes the glycosuria ceases, the patient becomes tolerant of carbohydrates, the sugar content of the blood decreases as the disease progresses, and the glycosuria reappears if the

cancer is excised. Indeed, in 9 cases, in spite of complete destruction of the pancreas by cancer, no glycosuria appeared. A. Braunstein (Klin. Woch., Apr. 29, 1924).

It is Warburg's idea that in oxygen deficiency (produced by pressure, sclerosis, action of bacteria or other influence) certain cells which are not able to glycolyze live by utilizing energy set free by the glycolysis and grow at its expense. The lactic acid present gives the growth stimulus. Perfusion of the growth with oxygen or alkali might perhaps neutralize this growth tendency apparently produced by action of the organic acid upon the tumor cell.

Here it is opportune to note the relationship of *organic acids* to tumor formation. Auler (Zeit. f. Krebsf., xxii, 392, 1925), in his studies of tumor formation in plants, found that if the stem of a plant is kinked, so that the up and down movement of the metabolic products and the respiration are hindered, there occurs at the place of injury a stagnation of nutritive and organic acids, which give rise to callus at the location of the injury. As soon as the disturbance is removed, the local overgrowth ceases. In this the condition differs from human cancer. The chlorophyll cells of which the tumor is formed are so poor in chlorophyll that the tumor on section is as white as is a cancer. They have not lost, however, the ability to differentiate, so that on transplantation they grow and produce leaves with normal chlorophyll content.

Because of the lower biological level of plant cells, their great adaptability to live under difficult conditions, and their transplantability from one species of plant to another, it is difficult to compare tumors of plants

with those of animals; especially so in the contrast of their malignancy, since the same rules and standards are not applicable to both.

Related to the apparently direct production of increased amounts of acid in carcinoma patients is the apparently increased alkalinity of the venous blood. The average of twelve determinations on normal blood, as made by W. H. Chambers (Jour. of Biol. Chem., lxxv, 397, 1925) was pH 7.29; in 23 determinations on cancer patients it was pH 7.34. He concludes that there is no evidence of an actual decrease in the blood of carcinoma patients which can be related primarily to cancer. In 45 cases of carcinoma, the dialysate from the venous blood at 20° C. averaged pH 7.45, which was more alkaline than in normal subjects (pH 7.31).

In contradistinction to the above, C. F. and G. T. Cori found that the carbon dioxide power of the plasma of a chicken had the same values, but that the blood which passed through a tumor growing on one wing contained on an average 23 mgm. less of sugar and 16.2 mgm. more of lactic acid than the blood which passed through the normal tissues of the other limb. Plasma of blood of the involved side had 3.7 volumes per cent. less of carbon dioxide than that of the normal side. Plasma of blood of the involved side collected under oil had but 0.7 volume per cent. less of carbon dioxide than that of the normal side.

*Iodine and adrenalin* were found in experiments *in vitro* to be adsorbed more strongly by cancer cells than by other tissue. J. Carra (Tumori, Oct. 15, 1923).

Mice fed on food lacking in *vitamins* exhibited a resistance to cancer inoculation as compared to control animals. F. Ludwig (Schweiz. med. Woch., Mar. 6, 1924).

Overfeeding with *glucose* or injection of *insulin* was observed to be followed by rapid development of cancer in

rats. M. Händel and Tadenuma (Münch. med. Woch., June 27, 1924).

The growth of mice cancers was seemingly favored by the feeding of *potassium*, and slightly hindered by *calcium*. M. Händel (Zeit. f. Krebsf., July 15, 1924).

**Immunity in Cancer.**—There is undoubtedly a certain small percentage of primary cancers in man which regress. According to Carter Wood (Jour. Amer. Med. Assoc., Oct. 3, 1925), the "tumors resembling sarcomas but difficult to differentiate microscopically from the granulomas are the type most likely to regress." The X-ray for a time was thought to produce immunizing effects. Opitz, with this idea in mind, radiated the entire body, but produced no better results (Wood). Caspari (Zeit. f. Krebsf., xix, 74, 1923) thinks the death of cancer cells sets free a non-specific substance which interferes with the further growth of the tumor. Regaud also believes that a toxic substance with a lethal effect on the tumor is set free. Carter Wood, concluding from his experiments, states that the body plays no part in the destruction of the tumor by irradiation.

Murphy and Morton have shown that mice naturally refractory to transplantable mouse cancer exhibit a marked lymphocytosis which is absent in the susceptible animals. Murphy, Nakahara, and Sturm (Jour. of Exper. Med., xxxiii, 423, 1921) undertook to stimulate cancer immunity by 2 agents influencing the lymphoid structures, *viz.*, small doses of X-rays and applications of dry heat, the latter of which proved the more effective. Whereas normal mice inoculated with cancerous tissue showed an average immunity of 16.5 per cent., mice to which dry heat had been applied one week before the inoculation showed an immunity of 60.3 per

cent.; in mice X-rayed 3 to 7 days before inoculation the immunity was 37.5 per cent. The immunity was found to vary directly with the amount of stimulation of the lymphocytes existing at the time of the inoculation or immediately after it.

**SYMPTOMATOLOGY.**—The symptomatology of cancer depends so greatly upon its location that it cannot be taken up in detail in a review of this kind, but certain general features may be mentioned.

In the large majority of cases the appearance of a tumor or "lump" is the first feature to attract the attention of the patient; the only exception to this statement relates to growths in the internal organs, and even among these a tumor may be the first symptom noticed by the patient, but more frequently it is a disturbance of the function of the organ affected that first attracts attention. Even in the latter case careful examination by the physician usually reveals a tumor, although instances are constantly occurring in which a malignant growth has not been diagnosed until an autopsy has been performed. Such a condition is more apt to exist when the primary tumor remains small, and the secondary growths far outstrip it in rapidity of growth, or when, from the location of the primary growth, it interferes, even when of small size, with the function of some important organ.

An illustration of how the first of these conditions may obtain is furnished by a case coming under the observation of Janeway. In this case a primary epithelioma of the antrum escaped notice until only a few weeks before the patient's death, while the metastases in the lymph-nodes, which had been present two years before death, and which had been operated upon two or three times, had been regarded as the primary tumor.

Illustrations of the second class of conditions are furnished by certain *cancers* occluding the common bile-duct, the pyloric opening of the stomach, or the intestinal lumen, and even diffuse cancer of the whole gastric or intestinal wall, or one involving the head of the pancreas. In neoplasms of the internal organs it is a disturbance of the function of the organ that almost always first calls the attention of both patient and physician to the disease. For detailed description of such growths the reader is referred to articles on the various organs; it is the scope of the present review to outline in a general way the main features of cancer, but a few illustrations may be given. Thus, in carcinoma of the esophagus the first symptom is dysphagia; in the carcinoma of the stomach there is a disturbance of gastric digestion or symptoms of pyloric obstruction; in malignant disease of the head of the pancreas or bile-duct, obstructive jaundice occurs; in the intestines, there will be chronic intestinal obstruction; in carcinoma of the rectum we have constipation, or bleeding or discharge from the anus. Hemorrhage from carcinoma of many organs often constitutes the first symptom, and this is especially true of carcinoma of the uterus and bladder.

The character of the swelling in internal cancer may or may not give diagnostic information; in many instances it aids materially. There is often present a certain firmness and nodular character to the surface, which belongs to cancer alone. On the other hand, the character of the tumor is of the greatest importance in all external growths and in the directly examinable superficial internal growths. In describing these it will be necessary to distinguish between sarcoma and carcinoma.

Peripheral *sarcomata* always first appear beneath the skin, or in direct connection with some bone, either filling its medullary cavity or growing from its periosteum; the tumors may attain considerable size before involving the skin or ulcerating through its surface. The consistency of *sarcomata* varies greatly, according to the character of their cellular elements. The osseous system forms a special site of predilection for sarcoma. When growing in the medullary cavity it gradually distends the latter, producing a fusiform swelling around the whole circumference of the bone; as the tumor increases in size the shell of bone around it becomes thinner and thinner, until finally there is a mere crepitating layer of bone, and spontaneous fractures are of frequent occurrence. It is, however, astonishing how large a size these tumors may attain before such an accident occurs.

When sarcoma grows from the periosteum it produces a fusiform swelling on one side of the circumference of the bone to which it is attached. The surface of these tumors is generally quite even, and the fusiform character of the swelling is not interrupted by nodular irregularities. The rapidity of the growth varies greatly, but massive tumefaction usually occurs, and this is one of the distinguishing features between sarcoma and carcinoma. The whole disease may run its course in four months or even in two, but in the more slow growing tumors it may last for years. Hemorrhages are of frequent occurrence, either in the interstices of the tumor or upon its surface after ulceration.

The degree of pain varies greatly in sarcoma; in rapidly growing tumors it may be considerable, and in the very

rapid ones it may be so severe that the disease can be mistaken for osteomyelitis; in slower growths it often does not amount to more than a dull ache, even after the neoplasm has attained some size.

It is unusual for the neighboring lymphatic glands to become involved in sarcoma; metastases occur in distant organs by the path of the blood-vessels, as described in the section on Pathology; the lungs are usually first and most extensively involved by the metastases.

Sarcoma originating in subcutaneous connective tissue is commonly of a benign type. At first it generally forms a well-encapsulated tumor, with a very definite contour, only slightly nodular; as is characteristic of sarcoma in general, considerable size may be attained before the skin is infiltrated and becomes attached to the growth. In other words, the tumor originates beneath the skin, and this forms an important diagnostic criterion between sarcoma and carcinoma. The actual size which the neoplasm attains before the skin is involved depends upon how far beneath the skin it originates, and many of the deeper tumors may reach the size of an orange or a child's head before ulceration occurs. On the other hand, some may become attached to the skin when only the size of a pea or small nut, but even in such instances ulceration is delayed for a longer time than would be the case in epithelioma.

Another distinguishing feature between sarcoma and carcinoma is the age at which the disease develops. It is undoubtedly true, within certain limits, that both sarcoma and carcinoma become more frequent as age advances, but it is also true that sarcoma appears at a much earlier period than carcinoma.

Isolated instances of carcinoma may occur in young children, and we ourselves have seen epithelioma of the face as early as at 18 years of age. But it is not at all unusual for sarcoma to be found in babies, and it is of frequent occurrence in the second decade of life.

The appearances of carcinoma are, perhaps, even more characteristic than those of sarcoma. This is largely due to its early ulceration, and to the very typical character of the latter. We may limit our description to epithelioma of the skin and use this as a type of the disease.

In the very earliest stages of *epithelioma* there may be nothing more than a rose-colored dot of congestion, or a little excrescence, or roughening or scaling at one circumscribed spot. Hyperkeratosis seems to be a constant feature of the early stages of the squamous-cell variety, so that in these cases the earliest symptom is a persistent scale, which later appears as a scab, now and then dropping off and generally leaving a bleeding surface. The basilar-cell epithelioma, on the other hand, usually begins as a minute, solid nodule, and this gradually enlarges so that there is a definite stage of solid tumefaction before ulceration occurs. The basilar-cell epithelioma may then form circumscribed ulcerations of a characteristic appearance, or it may spread first beneath the epidermis over a large area without ulceration. After ulceration has occurred the same description may apply to both the basilar and squamous type of tumor.

The ulcer of epithelioma presents a crater-like appearance; the edges are raised and definitely indurated; the whole growth has a minutely nodular surface, and this characteristic is par-

ticularly well developed in the raised peripheral border. Preserving these characters the ulcer increases in size by spreading at the periphery; the tendency for epithelioma of the skin to invade the deeper structures is very slight.

Epithelioma of this basilar-cell type is of very slow growth. Its progress may be insignificant during a period of even ten or twenty years; usually, however, during five years' time it becomes threatening. The squamous-cell variety, on the other hand, is much more rapid in its growth, and in one year's time it can become very dangerous. This type also invades the tissues more deeply, and it is this form of tumor which attacks the mucous membranes. Epithelioma of the tongue and walls of the oral cavity are of this type. Its greater degree of malignancy is also manifested by the frequency with which it forms metastases; these metastasizing forms are so rare in epithelioma of the basilar-cell type that they are curiosities, but in at least two personal cases metastases have been present. In the squamous-cell epithelioma metastases are of regular occurrence; the regional lymph-nodes are first involved, and, if life is prolonged, metastases occur in other portions of the body before death takes place from the local disease.

From epithelioma of the tongue and the walls of the oral cavity metastases rarely get beyond the regional lymph-nodes, and this constitutes one of the safeguards against this most deadly form of tumor. In the majority of autopsies personally performed, death has generally been due to exhaustion from local recurrence and recurrence in the regional lymph-nodes; metastases have not been present in other portions of the body.

The symptoms, then, of the later stages of squamous-cell epithelioma of the skin or mucous membrane consist in the rapidly growing, characteristic ulceration, the enlarged regional lymph-nodes, a gradual emaciation and development of cachexia, and foul discharges, with repeated hemorrhages from the tumor which exhaust the patient's strength. The absorption of toxic products the result of saprophytic bacteria and of the products of proteolytic enzymes induces a systemic intoxication; this toxemia may be accompanied by a low grade of fever, and is always partially responsible for the progressive loss of flesh and strength. As the growth increases in size and presses upon the neighboring terminal nerve twigs, it causes constant pain, which still further exhausts the patient; through these various means death ensues.

Perhaps the most characteristic train of symptoms occurs in *cancer of the breast*. We first have the occurrence of a lump; this is movable with the breast upon the deeper layers of muscles, and the skin can be freely moved over it; there may at the same time be some pain or discomfort. Slowly the lump increases in size, and the skin begins to be wrinkled and drawn in. The nipple is retracted and drawn to the affected quadrant, and the tumor moves less freely upon the deeper tissues. Palpation at various times from the onset will reveal nodular enlargements of the axillary lymphatic glands, and later on of the supraclavicular glands. Finally, the skin necroses from pressure, and the tumor-tissue is exposed by ulceration; in the meantime the neoplasm has been steadily increasing in size, and hemorrhages occur from slight traumas. The pa-

tient finally succumbs by exhaustion due to these processes, or from interference with the function of important internal organs, as the lungs, liver, etc.

In case of extensive lymphatic involvement, the tissues beneath the clavicle become thickened and less freely movable over the subjacent tissues than on the opposite uninvolved side. In order to elicit this phenomenon, the palmar surface of the fingers is placed on the chest above the involved breast and is gently moved from side to side. On the involved side the tissues do not slide as well as on the sound side.

These processes vary greatly according to the type of tumors; in six weeks' time, and even less, we have observed the development of an inoperable tumor with all the characteristic symptoms. On the other hand, where the neoplasm is composed of much fibrous connective tissue, years, even ten or twenty, may elapse before serious conditions are reached.

Where lumps in the breast are multiple, the lesion is not a carcinoma. Multiple carcinomata are so rare that they may be disregarded. Where a secondary carcinoma occurs it undoubtedly is a metastasis from the other breast. R. Johnson (Brit. Jour. of Surg., Apr., 1925) had four cases in which either preceding or subsequent to examination the patient had carcinoma of the uterus or ovaries.

The symptoms as well as the pathology of *melanoma* of the skin deserve separate consideration; these tumors form a very definite class by themselves, and certain peculiarities which they present, both pathologically and clinically, render them of special importance. The nature of their early stages has been the subject of much discussion, but, as already stated, they are com-

monly believed to originate in the so-called non-vascular nevi and pigmented moles. The ordinary harmlessness of these small affairs is well recognized, for the vast majority of them remain as such throughout life. Every now and then, however, one will begin to increase in size, and such a patient will ultimately die of generalized melanoma. When one of these tumors begins to increase in size, it commonly does so very rapidly, and from the start the tumor is most malignant. Metastases occur very early and are very apt to form in the skin, so that the surface of the body may be covered with multiple, pigmented nodules. The neighboring lymphatic glands are also very frequently involved, so that these tumors present quite an exception to the usual history of other forms of sarcoma. When the primary tumor occurs in the eye, the growth breaks through the sclera into the orbit; it also follows the optic nerve backward, and secondary processes develop within the cranium. In their very malignant tendencies, coming on suddenly after long periods of quiescence, these tumors form a class entirely alone.

The clinical course of lymphosarcoma is more appropriately treated under diseases of the lymphatic system, and that of the malignant adenomata under diseases of the various organs.

The status of *fever* as a manifestation of cancerous disease has been studied by W. Gordon (Lancet, cxcviii, 1309, 1920). He divided the cases into 3 groups, characterized, respectively, by (1) either "growth fever" or "complication fever"; (2) "complication fever" only, and (3) absence of fever. The first group includes cancer of the liver, stomach, suprarenals, lung, mediastinum, long bones, and, rarely, the breast. Fever may persist for weeks in primary carcinoma or sarcoma of the liver and differentiation from abscess may therefore be

difficult. Suppurative cholangitis may be associated with cancer of the liver and be an adequate cause of "complication fever." In the second group are commonly cancers of the gall-bladder, bile ducts, intestine, appendix, uterus, fallopian tubes, ear, and neck glands. In all these there is usually an associated infection causing fever. In the third group are cancers of the kidney, ovary, vulva, testes, penis, urethra, parotid, jaw, brain, spine, skin, muscles, heart, and pericardium. Hypernephroma is attended with fever, while renal tumors are not.

In 238 cancer cases, fever was observed at some time in 38.2 per cent., independently of any known complications. The highest percentage of fever was in growths of the lung and liver, while in the case of other organs the fever incidence was rather close to 33 per cent. Isolated rises of temperature were noted chiefly. Metastases did not seem to influence the incidence of fever. L. H. Briggs (Amer. Jour. Med. Sci., Dec., 1923).

Case in which fever occurred in regular waves of 7 to 12 days, each febrile attack presumably corresponding to a cancerous invasion of the blood-stream, since no septic complications were found at the autopsy. Anemia was severe in this case, eventually becoming pernicious. M. Roch and G. Bickel (Bull. Soc. méd. des hôp. de Paris, June 1, 1923).

*Itching* deemed of significance as a premonitory symptom of malignant disease. Two cases of cancer of the stomach complained of increasingly severe generalized pruritus for several months before the first gastric manifestations of cancer appeared. H. Küttner (Zent. f. Chir., Apr. 19, 1924).

**Duration of Cancer.**—There is considerable difficulty in estimating the actual duration of cancer. Few patients recognize the actual beginning of the disease. A study of the disease from this standpoint reveals that death rarely occurs as a result of the disease itself, but in almost every instance is due to some mechanical cause, as a stenosis,

compression, perforation, or hemorrhage. Very frequently also the first symptoms of the disease are of a mechanical nature, the disease remaining absolutely latent until the function of some important organ is interfered with. The beginning of the disease and the occurrence of the first symptoms seldom coincide. The disease is shortest in cancer of the orifices of the digestive tract and longer in cancer of larger cavities. Often a short course will mean a latent period.

The following table, copied from Carl Otto (Second International Congress on Cancer, 429, 1910), from whom the above conclusions are also taken, illustrates these points for cancer of the digestive tract:—

	Esophagus.	Cardia.	Stomach.	Pylorus.	Intestine.	Pancreas.	Biliary system.
1 to 14 days .....	7	..	1	1	5	..	..
1 month .....	7	..	5	1	..	..	..
2 months .....	10	2	16	6	4	7	3
2 to 4 months .....	14	4	12	8	6	16	3
4 to 6 " .....	11	5	8	7	7	5	2
6 to 8 " .....	6	2	2	4	3	9	1
8 to 10 " .....	1	1	2	2	4	..	..
10 to 12 " .....	1	1	1	6	2	1	..
1 to 4 years .....	5	2	4	6	4	..	3
At autopsy .....	1	..	8	4	..	1	..
No clear cases .....	2	..	2	5	2	..	3
Totals .....	58	17	61	50	37	39	15

**DIAGNOSIS.**—In the physical examination of a cancer patient great care should be exercised to use no manipulations which might cause trauma. Simpson states that the unfavorable results in cancer of the breast are due to premature metastases brought about by excessive handling, both by the patient and physician.

Aside from the aid in the diagnosis of cancer to be obtained from the

Thiem gives the following table, showing the duration of cancers of various organs:—

Duration of cancer.	First subjective symptom to diagnosis	From time of diagnosis to death.	Total development time.
	Months	Months	Months
Gall-bladder cancer .....	4.2	4.0	4.6
Liver cancer .....	4.7	2.7	7.4
Esophagus .....	6.0	4.0	9.3
Uterine .....	6.2	4.4	10.6
Stomach .....	7.0	1.8	8.8
Throat .....	7.5	1.5	10.0
Intestine .....	8.6	4.5	13.1
Breast .....	9.1	....	19.2
Various skin .....	8.0	..	..
Larynx .....	8.9	..	..
Legs .....	25.0	..	..
Face and head .....	45.6	..	..

clinical features of the growth, the characteristic appearances or objective symptoms of the disease in its various locations and forms, and the general subjective symptoms, many attempts have been made within recent years to perfect some clinical test pathognomonic of cancer, which would enable us to diagnose the disease early.

The writer found—and his view has been confirmed by Blumenthal and others—that in suspected malignant growths, a rise of temperature following a rectal injection of potassium iodide (4 Gm.—1 dram—with sodium bicarbonate 2 Gm.—½ dram—and water 90 c.c.—3 ounces) differentiates malignant growths from syphilis. M. P. Michailoff (Roussky Vrach, Apr. 6, 1913).

Both the urine and blood have been extensively investigated for changes characteristic of cancer.

Fuld found that in carcinoma pepsin is absent in the urine, while in other pathological conditions which might be confused with cancer, even in achylia gastrica, pepsin is present in the urine.



A *urinary methylene blue test* has been described by J. Fuhs and W. Lintz (Néoplasmes, Mar. and Apr., 1923). A little Loeffler's methylene blue is added to the urine and the latter incubated for 12 or 24 hours. Decolorization occurs in cancer cases and a few other conditions, such as acute rheumatism and nephritis.

**Acid Oxyproteid Test.**—Salomon and Saxl (Wien. klin. Woch., xxiv, 449, 1911) demonstrated an increase of oxyproteid acid in the urine of patients in whom carcinoma is growing. A number of other conditions, however, particularly severe liver diseases, abscess and cirrhosis, enlargement of spleen, and pregnancies, will also give an increase in this same substance. Acid oxyproteid is a polypeptide, and Sorensen introduced a simple method for its estimation by titrating with formol. Of 81 cases of cancer, 61 gave a definite positive test, 10 a weak reaction, and 10 were negative.

Regarding the Salomon-Saxl test for neutral sulphur in the urine, M. Romani (Gior. di clin. med., Feb. 10, 1922) obtained only 40 per cent. of positive reactions in 30 cancer cases. He concludes that this test is not specific for cancer and appears only in advanced stages, when the condition is easily recognized in other ways.

**The blood** has been investigated by a variety of pathological procedures in attempts to find an early specific test for cancer. Crile (Jour. Amer. Med. Assoc., li, 158, 1908) attempted to show that in over 90 per cent. of cases the blood-stream of cancer patients had the power of destroying the red blood-cells of a normal individual when they were washed and suspended in physiological salt solution. No one else was able to confirm Crile's results.

A study of the leucocytes with relation to their form, ameboid movement, death form, etc., in cases of malignant disease led the writer to the following conclusions: If the smear shows neutrophilia and fat drops in many of the neutrophils, and if the nuclei of the neutrophils are largely multifid, the case is one of a coccal infection of great or very great severity. If the smear shows a relative abundance of lymphocytes (especially of the very small variety); if there is no leucocytosis, and if multifid nuclei preponderate, the case is almost certainly not one of malignant disease. If there is neutrophilia, with bizarre forms, or pseudopods in number; if the lymphocytes are in many instances showing ameboid outlines, and if the monocytes show ameboid nuclei, the case is almost certainly one of malignant disease. Gruner (Brit. Jour. Surg. Jan., 1916).

In the differentiation of cancer from *achylia gastrica* the leucocyte count is of some significance. Among 67 cases of achylia the writer found leucopenia in 23 and leucocytosis in 7, the remainder being normal; in 68 cancer cases the corresponding figures were 15 and 27, leucocytosis, therefore, favoring a diagnosis of cancer in otherwise doubtful cases. Considering only the lymphocytes in the differential count, on the other hand, lymphocytosis pointed to achylia and lymphopenia to cancer. Weinberg (Deut. med. Woch., July 21, 1921).

**Antitryptic Index.**—Blood-serum possesses the power of inhibiting the digestive action of trypsin. In general, the principle of the reaction consists in estimating, upon plates or tubes of casein or beef-serum, the digestive action of a 1 per cent. solution of trypsin mixed with the blood-serum to be tested, diluted to varying degrees, and comparing its digestive action with similar strengths of trypsin unmixed with serum.

Katzenbogen (Berl. klin. Woch.,

xlvi, 1840, 1911) came to the following conclusions: 1. All patients in whom there is a considerable destruction of leucocytes, pancreatic disease, suppurative conditions, pregnancy (placental ferments), or cancer show a high antitryptic index. 2. If clinically it is impossible to distinguish between a benign and malignant new growth, a high antitryptic index is to be regarded as a decisive factor. 3. In suppurative conditions a high index indicates a favorable prognosis, and *vice versa*.

The writer examined (by the Roger and Savignac methods) the action of antitrypsin on 32 patients whose cases were either diagnosed clinically as cancer cases, or proved to be so at the necropsy. Sixty-three per cent. proved positive. The activity of antitrypsin was greatly influenced by the position of the cancer, and by the degree of cachexia. When the cancer developed in an alimentary organ such as the stomach, or the liver, the increased activity of antitrypsin in the serum was remarkable; while in the case of cancer of the uterus or penis, the increased activity was comparatively small. In the case of non-cancerous diseases, the activity of antitrypsin in the serum was either normal, or only a little increased, except in cases of pregnancy, puerperal women, chronic suppuration, and pulmonary tuberculosis, in which increased activity of antitrypsin in the serum is a recognized fact. Kurata (Bull. of Naval Med. Assoc., Tokyo, Aug., 1917).

#### Complement Deviatory Power.—

Caan (Münch. med. Woch., lviii, 731, 1911) tested the blood for its complement deviation power in cancer by a procedure analogous to the technique of the Wassermann reaction in syphilis. Of 85 cases, 35, or 41 per cent., gave a positive result, though a weak one.

The activation by cobra venom of the hemolytic action of the serum in the deviation of complement test occurs only with serum from persons with malignant disease. With rabbit red corpuscles, a positive reaction was pronounced in the writer's total of 53 out of 64 persons with carcinoma. In all the other 11 cases, the reaction occurred, but not until after the 20th hour, and these are considered negative. In 62 persons with benign tumors there was no trace of a positive reaction. He now uses 0.1 c.c. (1½ minims) of a 1 to 20,000 solution of cobra venom, *e.g.*, 1 part of a 1 to 5000 solution of venom in 3 parts of normal saline. C. B. Farmachidis (Riforma Medica, May 18, 1918).

Von Dungern (Münch. med. Woch., lix, 65, 1912) described what seemed to him a dependable test along these lines. He uses extract of the tumor tissue obtained with 98 per cent. ethyl alcohol, allowing 6 times as much alcohol as tumor tissue and extracting from 12 to 8 hours. This is diluted with an equal quantity of normal salt solution to which is added ½<sub>20</sub> c.c. of serum to be tested, and, as complement, guinea-pig serum, ½<sub>20</sub> c.c. He uses cows' blood-cells capable of being dissolved by the serum, sensitized to such a degree that the solution of the cells follows in ¾ hour at 37°. He obtained a positive test in all cases of malignant tumors, 42 in number, and negative findings in all other conditions, 13 in number, except syphilis. Some benign tumors, however, especially one case of myoma, gave a positive result.

Fry (Brit. Med. Jour., July 4, 1925) favors a procedure of the nature of a colloidal flocculation reaction, dispensing with the hemolytic system. Breast carcinoma tissue is the antigen used. Five hundred serums were tested. In 239 cases of malignant disease positive flocculations were obtained in 71 per

cent. In 261 controls, comprising healthy individuals, cases of non-malignant neoplasms, and medical and surgical conditions, a negative result was obtained in 78 per cent. All healthy individuals but 1 were negative; non-malignant tumors were usually negative; in acute febrile conditions, such as tuberculosis or sepsis, positive results may occur.

**Cytolytic Power.**—Freund and Kaminer (Wien. klin. Woch., xxiii, 1221, 1910) reported that serum from cancer patients fails to dissolve the patient's cancer cells when in contact with them at 37° for twenty-nine hours, while normal serum possesses such a power. Neuberg and Stammeler confirmed these findings, but others reached contradictory results.

A serum is considered as possessing normal cytolytic power against cancer cells when the number of such cells, suspended in salt solution and mixed in proper proportions with the serum, is reduced after contact to 50 per cent. in comparison with the controls.

Monakow obtained a positive reaction in 86 per cent. of cancer cases. Of 52 sera from non-cancerous individuals 13 acted as the 86 per cent. of cancerous sera had, *i.e.*, failed to dissolve 50 per cent. of the cells, and 5, or 9.6 per cent., were doubtful. Only 65.8 per cent. of the controls dissolved 50 per cent. or more of the cells. He concluded that with care the reaction is a diagnostic aid.

**Meiostagmin Reaction.**—This appears to be the most important of all of the general reactions of cancer.

The reaction measures the change in the viscosity of dilutions of serum from cancer patients resulting from the mixing and incubating of the same for two hours with a properly diluted antigen

obtained by extracting the dried tumor tissue with methyl alcohol. Five Gm. of dried tumor tissue are extracted with 25 c.c. of methyl alcohol.

This is diluted 100 times and 1 c.c. of such a dilution is mixed for the purpose of the test with 9 c.c. of a 1:20 dilution of the serum in 85 per cent. sodium chloride solution. The addition of acetic acid in quantities to make a proportion of 1:1000 of acetic acid in the total mixture increases the intensity of the reaction.

The difference of superficial tension between the test mixture and its control is measured by a viscometer, Traube's stalagmometer being a convenient one.

Ascoli and Izar developed the test (Münch. med. Woch., lvii, 62, 403, 954, 1170, 2129, 1910), and obtained out of 100 cases of malignant new growths 93 reactions which gave a sufficient change in superficial tension to be designated as positive, while they failed to obtain such a change in all of 103 cases of various other non-cancerous diseases. Various authors have in the main confirmed Ascoli and Izar's results.

**Reaction in Vivo.**—Subsequently Izar (Berl. klin. Woch., xlviii, 1748, 1911) improved his technique and so modified the test that the reaction is conducted *in vivo*. The reaction *in vivo* depends upon the fact that an aqueous emulsion of either a methyl alcohol or ethereal extract of tumor tissue which is treated for either one hour at 50° or two hours at 37° is found to develop peculiar active toxic properties. When an antigen extracted in the manner described is mixed with blood-serum and heated for one hour at 50° and then centrifuged, it is found that a toxic principle is developed in either the precipitate or filtrate, according as the

serum is taken, respectively from an individual suffering from cancer or from a normal person.

The toxicity of the precipitate or filtrate is tested by injecting it into either rabbits or guinea-pigs. Such animals, after injection, develop dyspnea, convulsions, vomiting, rectal evacuations, paralysis of the extremities, and death, if the test is positive within twenty-four hours. Izar at first tested 21 definite tumor cases, 19 of which gave a positive reaction. Of 32 non-cancerous patients 2 gave a positive reaction.

Contrasting this reaction with the meiostagmin reaction conducted *in vitro*, he obtained, out of the same 53 cases, identical reactions in 48 cases, with the exception of 5, so that in the same series of cases the meiostagmin reaction *in vitro* gave 5 more anomalous results than the reaction conducted *in vivo*.

According to N. Waterman (Nederl. Tijdschr. v. Geneesk., Nov. 12, 1921), only the miostagmin (or meiostagmin) test, among the older serodiagnostic methods, is of practical importance, and this, indeed, only if its reliability can be improved.

**Botelho's Serum Reaction.**—As described by Sabrazès and Muratet (Arch. des mal. du cœur, Dec., 1923), this test is performed as follows: Equal parts of fresh serum from the patient and of 0.75 per cent. sodium chloride solution having been mixed, 0.5 c.c. of this mixture is diluted with 2 c.c. of a solution consisting of citric acid, 5 Gm.; commercial formaldehyde solution, 1 c.c., and normal saline solution (or better, distilled water), 100 c.c. Then there is added 0.7 c.c. of a solution of iodine, 1 Gm., and potassium iodide, 2 Gm., in water, 210 c.c. A positive

result is shown by the appearance of turbidity on standing, while a negative result is confirmed by persistent clearness after further addition of 0.2 c.c. of the iodine-iodide solution. Sabrazès and Muratet found this test positive in about 75 per cent. of cancer cases. The response is also frequently positive in chronic myeloid leukemia, typhoid fever, Banti's disease and pregnancy. When it is negative, cancer is practically excluded.

Peyre (Bull. méd., Sept. 27, 1924) deemed this test of diagnostic service.

**Glucose Tolerance Test.**—The blood sugar tolerance was studied by Friedenwald and Grove (Amer. Jour. Med. Sci., Sept., 1920) in 32 cases of typical carcinoma of the gastrointestinal tract, in 17 of which the diagnosis was confirmed by operation. A rather characteristic curve of sugar tolerance differing somewhat from that observed in carcinoma of other regions of the body was found. The curve usually showed a high sugar content even in the fasting state, followed by an initial rise, up to 0.24 per cent. or higher, within 45 minutes after ingestion of the dextrose, remaining at this level for at least 120 minutes and at no time during this period falling below 0.20.

The technique of this test, as described by H. M. Feinblatt (L. I. Med. Jour., July, 1921), consists in giving the patient 100 Gm. (3½ ounces) of glucose (dextrose) in black coffee after a night's fast. Vein puncture is carried out 5 minutes before giving the sugar, and again 45 minutes and 2 hours after administration. Each time 5 c.c. of blood are drawn into a tube, containing a few crystals of oxalate, and then promptly analyzed ac-

cording to Folin's new microchemical method. From tests in 56 cases Feinblatt concluded that while lowered sugar tolerance may be present in many diseases other than gastrointestinal carcinoma, they generally do not give the clinical symptoms or physical signs of carcinoma and may easily be ruled out. The test is of distinct value in the differential diagnosis between carcinoma and other gastrointestinal diseases. The patients with carcinoma of the stomach or alimentary tract invariably showed hyperglycemia.

Glucose tolerance test used in 15 cases of cancer in which the diagnosis was definitely proved. Of these, 10, or 66% per cent., yielded a sustained typical or atypical blood sugar curve of diagnostic utility. S. K. Simon and J. H. Smith, Jr. (So. Med. Jour., Aug., 1923).

Following are a number of other tests which have been advocated:

Loeper (Presse méd., Apr. 27, 1921) has called attention to a *hyperalbuminosis* of the blood to be found in cancerous subjects. He contrasts this unusual protein content of the blood with the cachexia and low food intake in such patients. He found that the condition parallels the size of the tumor present, and considers it of diagnostic utility.

S. Gussio (Tumori, Aug. 5, 1923) found the *serum globulin* always increased and the *serum albumin* decreased in cancer. In debility from other causes a similar tendency was seen, but in cancer the abnormality was more marked and earlier in advent, occurring while the general health was still but little affected.

R. Fischer (Bull. de l'Acad. de méd., Jan. 16, 1923) has described a test based on the fact that *coagulation of the serum by alcohol* is less pronounced after addition of 1:500 *gelatin solution* than after addition of normal saline solution in early cancer, cachexia and paroxysmal hemoglobinuria, whereas in other conditions the converse is the case.

V. E. Mertens (Deut. Zeit. f. Chir., May, 1923) observed that *intracutaneous injection*

*of serum from cancer patients under X-ray treatment* caused a characteristic local reaction in the form of a purplish spot in other cancer cases. F. Hoff and K. Schwarz (Münch. med. Woch., June 20, 1924) confirmed this, 14 cases giving a positive response at some time, while all but 3 of 17 controls were negative.

J. Thomas (Monde méd., June 1 and 15, 1924) had found, with M. Binetti, that serum from a cancer case, mixed with tumor extract, *decolorizes* a glycerinated solution of *methylene blue* much more rapidly than normal serum. He reports a number of cases illustrating the value of this test in the diagnosis of doubtful cases of malignancy.

According to W. Simon (Zent. f. Gyn., Oct. 25, 1924), *alimentary leukopenia* occurs in 90 per cent. of all cases of cancer of the female reproductive organs. This may be of diagnostic and prognostic service. H. Seidl (Münch. med. Woch., Dec. 5, 1924) has confirmed Simon's observations.

*Blood sedimentation* was found always accelerated by Gragert (Arch. f. Gyn., Apr. 16, 1923) in 70 cases of cancer of the female reproductive organs. He regards this as reflecting a toxic action of the tumor on the system, but sedimentation did not return to normal until over a year after removal of the tumors. Roffo (Prensa méd. Argent., July 10, 1924) similarly found sedimentation greatly accelerated in 101 cancer cases as compared to 33 persons either normal or with non-cancerous conditions. Early superficial growths, however, did not affect sedimentation. Troise, de Marval and Rovere (Semana méd., June 26, 1924) observed a slowly progressive acceleration of sedimentation in cancer, while in *hydatid disease* there was no acceleration until suppuration set in, when abrupt acceleration occurred.

**Other Diagnostic Aids.**—Various other aspects of the clinical laboratory diagnosis of cancer have been well set forth by James Ewing (Jour. Amer. Med. Assoc., Jan. 3, 1925). The *frozen section* immediately reveals the nature of many tumors, but usually only those which an experienced pathologist can recognize by gross examination. It can be applied only to those portions of tissue which are selected as most suspicious. Having made more errors by the frozen section method in breast cases than by the

gross examination, Ewing has not employed it in this field for many years. As a rule, tumor tissue and infiltrated structures present features easily recognized by **sight and touch**. When papillary adenomas arising in cysts become cancerous the fact is revealed by greater opacity, chalky streaks, and fixation of the capsule of the cyst. Axillary lymph-nodes, atrophic, but invaded by fat tissue and very firm and encapsulated, are often mistaken for cancerous nodes. True cancer renders the nodes rigidly hard and very opaque.

**Roentgenography** has greatly enlarged the opportunities for the study of the gross anatomy of tumors. It should correspondingly diminish the indications for biopsies and exploratory operations. Few bone tumors cannot be somewhat accurately classed by means of roentgenograms and clinical signs.

The indications for a **biopsy** are in inverse proportion to the skill and experience of the surgeon and pathologist in interpreting the gross signs of tumors. Yet often it is indispensable. Removal of a small, carefully selected portion of an accessible tumor seldom does harm, though cutting through the skin to excise a portion of a breast tumor is generally to be discountenanced. It is better to remove the whole tumor and follow immediately by the procedure indicated by the results of pathologic diagnosis. Incision of encapsulated malignant tumors growing under pressure is nearly always harmful. The therapeutic test by radiation is generally far better and safer. Incision into bone tumors is one of the last steps to be taken in diagnosis. The grounds for preferring the cautery over the sharp knife in biopsy have never been satisfactorily established, and Ewing prefers the knife.

Correct diagnosis may at times be made on the basis of **fragments of tumor tissue** found in the sputum, stomach washings, urine or other excreta.

Irregular bleeding from the uterus, however slight, calls for a biopsy. The author thus detected 8 cases of incipient uterine malignancy. If the hemorrhage continues, initial negative findings should not be held conclusive. Siredey (Bull. de l'Acad. de méd., July 10, 1923).

Interesting diagnostic aids from **radiation** have come to light. *Giant-cell tumors* of bone respond to external radiation by preliminary swelling followed by regression and restoration of the shaft, while most *osteogenic sarcomas* show no such changes or respond very slowly. Very cellular *myelomas* and other round cell tumors also yield promptly to radiation, while tumors that form bone or much interstitial tissue are resistant. Many *lymphosarcomas* melt down rapidly, while *Hodgkin's granuloma* is more resistant and generally leaves cicatricial masses. Simple hyperplastic *tuberculous lymph-nodes* gradually recede under radiation, unless there is caseation and suppuration. Areas of *chronic mastitis* become swollen and indurated, while cancerous masses generally recede notably and leave very hard cicatrices.

Special diagnostic chemical tests have been devised for the early recognition of cancer of the stomach. These are more properly dealt with in that portion of this work which treats specially of the diseases of the stomach.

As regards "*internal cancer*" in general, however, it may be mentioned here that, as stated by O. V. Huffman (L. I. Med. Jour., July, 1920), all patients suspected of having such a growth should be given the benefit of: (1) A test breakfast and gastric analysis. The Rehfuess fractional analysis of gastric secretion and the examination for occult blood in both gastric contents and feces should be done. The Salomon and Wolf-Junghans tests for serum albumin should be made. The vomitus should always be examined and likewise the feces for blood, pus and necrotic material. (2) A complete X-ray study, especially fluoroscopic examination after an opaque meal or enema. (3) An exploratory operation if there is no restoration of health after 1 month of symptomatic treatment, inasmuch as the condition to be differentiated from cancer re-

quires operation as well, and because as soon as the diagnosis would be absolutely certain it is too late to operate.

**Abderhalden Test.**—This test, based on the assumption that the presence of certain morbid conditions, including cancer in any structure, brings about the formation of protective ferments, is referred to under HEMATOLOGY in the fifth volume.

**PROPHYLAXIS.**—As cancer is undoubtedly induced by chronic irritation, all sources of such irritation should be removed. There is no doubt that the pipe smoker and individual with irritating snags of old teeth are more predisposed to cancer of the mouth than are others; therefore, the pipe smoking should be stopped and irritating teeth should be removed. It is difficult to decide at times after a cheek cancer has developed from irritation due to snags of teeth whether, in the presence of such a cancer and its probable spread through the open fascial planes, it is advisable to recommend the extraction of such teeth.

As cancer is very prone to occur in the cervix uteri as the result of chronic irritation from ulcers resulting from lacerations, it is necessary that such ulcers be properly treated and cured by the gynecologist. The same criteria may be applied to internal organs. Wm. Mayo states, in referring to the gall-bladder, that "in nearly all the cases of cancer of the gall-bladder which we have had an opportunity to carefully examine, gall-stones were either present or there was evidence to show that they had been present" (Ann. of Surg., June 2, 1914).

Aniline workers are subject to can-

cer of the bladder. In such workers bladder irritation should receive immediate attention.

In the treatment of cancer one should remember that it requires almost as long a period for the retrogression of a tumor as for its production.

**TREATMENT.**—The subject of the treatment of cancer covers a wide field, and it is wide because we yet know so little in regard to the real nature or cause of the neoplasms which are grouped under this name. Pathology has not helped us much as to the reason for their appearance and malignant course, nor has it afforded us much guidance as to treatment, except to emphasize the necessity of very radical extirpation, including the glands and neighboring tissue when the knife is resorted to.

When we turn to the results of experimental work on animals, as already detailed, we find that, while some malignant tumors can be transmitted from one animal to another, under certain circumstances, in some mysterious manner, a degree of immunity can be also created under certain conditions of inoculation.

All experience shows that there is no internal remedy or remedies which will surely check the progress of the disease. All studies, however, point to the fact that there is some underlying hidden cause which leads to that aberration in the action of tissue-cells which we call cancer. It is possible to conceive of such an underlying hidden cause as residing in only the cells themselves, or in some abnormal chemical constitution of the plasma bathing the cells, or in both of these possibilities acting together. Careful research upon the metabolism

of cancer alone will help us to unravel these obscure problems.

The writer looks upon cancer as a general disease of which the local lesion, ordinarily excised surgically, is the result of a previous, perhaps long-standing, blood or nutritional disorder. Excision cannot be expected to eradicate the malady permanently. The secretions and excretions of the body, both in early and late cancer, exhibit departures from normal indicating metabolic disturbances which may influence the nutrition of the cells.

An absolutely **vegetarian diet** is needed in treatment and prophylaxis. It should be maintained indefinitely, excluding animal protein, even eggs and milk, though not butter, of which  $\frac{1}{4}$  pound is to be taken daily by a person weighing 150 pounds. Cereals are to be freely eaten, slowly, with a fork, and with butter, not with milk and sugar, though the latter may be used moderately where it seems necessary. Perfect mastication, with thorough insalivation, is essential. As beverages, only weak tea is allowed, with some postum or other coffee substitute. Sufficient water, not iced, should be taken, commonly  $\frac{1}{2}$  pint with each meal, and, hot, 1 hour before both breakfast and the evening meal. A simple, healthy life, with regular hours of eating and sleeping, and a reasonable amount of exercise, are important.

Medical treatment lies mainly along the lines of elimination, which is always faulty, both by bowel and kidneys, *viz.*, **cascara**, in combination with other remedies, and also, often, once a week, on alternate days, 2 laxatives of **blue mass**, **colocynth**, and **ipsecac**. For the kidneys, **potassium acetate**:—

℞ *Potassii acetatis* ..... ʒj (30 Gm.).  
*Tinct. nucis vom.* ..... ʒiv (15 c.c.).  
*Fl. ext. cascarae sagradae* ʒj-ʒiv (4 to 15 c.c.).  
*Fl. ext. rumicis* (N. F.) . ʒiv (120 c.c.).

M.—Teaspoonful in water  $\frac{1}{2}$  hour before eating.

**Iron and arsenic, phosphates and strychnine**, and even **codliver oil** are also useful. **Thyroid gland** sometimes assists materially in removing the growth, but must be given with caution.

These patients should be seen at least weekly, and even for months or years, with careful and accurate records, urinary and blood analyses, etc. From 40 years' experience the author is convinced of the efficacy of the above non-surgical treatment of cancer. L. D. Bulkley (Address before Soc. Alumni of Bellevue Hosp., Feb. 7, 1917).

Growth, ulceration and cachexia from human neoplasm were not affected by a diet of solac, which is free from fat-soluble vitamin A. Wyard (Lancet, Apr. 29, 1922).

In rats and mice, the rate of cancerous growths in the hosts was not altered if the diet contained over 8 per cent. of protein, whether of animal or plant origin. Ingestion of a protein-free diet caused marked diminution of tumor growths, accompanied by extreme malnutrition of the hosts. The malignant character of cancer cells cannot be influenced by the ingestion of high protein or protein-free diets or high carbohydrate or low carbohydrate diets. Oral administration of codliver oil, linseed oil and chaulmoogra oil had no influence upon tumor susceptibility. K. Sugiura and S. R. Benedict (Jour. of Cancer Res., June, 1925).

*Effect of Starvation of Host Upon Growth of Tumor.*—A neoplasm requires a certain amount of protein. This it acquires either from the food supply of the host or from the tissues of the host. It utilizes the former much more easily than it does the second, so that proportionately it grows more rapidly than its host, because the "tissues of a neoplasm can be built up with less protein than the same weight of host tissue and must grow more rapidly than the latter under circumstances at the same rate" (Cramer and Pringle, Proc. Roy. Soc., Ser. B, 315, 1909-10). Because of the utilization by the neoplasm of the tissues of its host as protein supply, it grows even when the host is starving.



The treatment of cancer is naturally divided into: I, surgical, and, II, non-surgical. By the former is intended the complete surgical removal of all accessible disease, both in the primary site and in metastases. The latter is understood to include all other measures which have been reported on more or less favorably, either for influencing advantageously the supposed constitutional condition underlying the activity of neoplasms or for directly attacking the latter.

**I. Surgical Treatment.**—In the light of modern surgical development, and of the results reported by able and conscientious observers and operators, there can be no question but that surgery has accomplished very much in the treatment of cancer. And it is believed that if competent surgery could have the opportunity of reaching the disease in its incipency the percentage of permanent successes would be even much greater. The possible achievements of surgery are illustrated by such statistics as those of Halsted in cancer of the breast, showing 42.3 per cent. of cures lasting over three years; by those of Kuster's clinic, reported by Haines, of cancer of the uterus, with 47.5 per cent. of cures lasting over five years, and those of the Mayo brothers, of 22.2 per cent. of cases of gastric carcinoma, alive and well for more than three years after operation. Confirmatory results have been reported for cancer of the breast by many surgeons.

The percentages above mentioned are simply illustrative of what can be accomplished, and are instructive when we consider the common course of such cases when left without surgical aid. They also teach a lesson in regard to public enlightenment concerning what can be done for malignant disease, and

in regard to professional education relating to the early diagnosis of such troubles. They likewise speak strongly in reproof of those, both in and out of the profession, who blindly condemn surgical operations, or who too often delay resorting to them until the disease is so far advanced that it is too late to expect favorable results.

A single word must, however, be added as to surgical procedures. In claiming for surgery such a measure of success it is understood that the necessary operations are performed after the most approved methods, and with a thoroughness far different from that belonging to older days; these are matters which cannot be entered into here, but which are of the utmost importance.

The end-results of 1000 operations for carcinoma of the abdominal viscera from the statistics of Bunts, Lower, and the writer's own work, showed that every possible **psychic aid** should be employed to **diminish all emotional stress** incident to the operation. **Nitrous oxide** is used as an anesthetic rather than ether, as it causes less marked changes in the brain, adrenals, and the liver, and at the same time protects them to a certain extent from surgical trauma. **Anoci-association** is employed throughout the operation, because operations done under this method show no increased acidosis. Crile (Interstate Med. Jour., xxii, 722, 1915).

Regarding the chances of recovery from cancer of the breast, the writer reviewed the literature and found: (1) Operation in early stages, modern methods, 12 recoveries out of 15 cases. (2) Operation in more advanced stages, modern methods with more extensive operation, 5 recoveries out of 15 cases. (3) Operation in later stages of disease, 1.5 recoveries out of 15 cases. The chances of survival in respect to age in breast cancer are: Women 50 years of age, no operation, 3½ years; late operation, 6¾ years;

early operation, 12 years. Average expectancy after operation, 10 years. J. E. L. Clayton (Jour. of Cancer Research, Apr., 1925).

Certain cases of cancer of the breast are doomed irrespective of the treatment. The writer believes that the use of the X-ray against a recurrence is of comparatively little value. Greenough (South. med. Jour., Mar., 1925).

The presence of a tumor in the breast, whether it is malignant or not, is sufficient evidence to justify an immediate operation. B. T. Simpson (N. Y. State Jour. of Med., Nov., 1925).

Surgical removal undoubtedly has its limitations, which are to be determined by competent judgment in each individual case; but these are gradually lessening with advancing knowledge and skill, and the percentage of permanent success is steadily improving in the hands of many competent operators. In superficial cancer or epithelioma, when well performed in the early stages, surgical removal gives a very large percentage of cures; indeed, when very radical and in a very early stage it may almost be said that the disease rarely recurs. In later stages there is, of course, a less measure of success, and, when far advanced, cancer of any form lies beyond the reach of surgery. In but few conditions is the success of prompt, careful, and radical surgical procedure more evident than in certain cases of epithelial cancer about the face. Even cancer of the tongue often yields brilliant results when thus rightly treated.

Report on 256 cases of *squamous-cell epithelioma* of the skin, constituting 12.8 per cent. of 2000 cases of general epithelioma observed in the Mayo Clinic from Nov. 1, 1904, to July 22, 1915. This type of epithelioma occurs more often in males, in the ratio of 4 to 1. The average age is 59 years. It was preceded by a mole, wart, pimple,

scab, ulcer, leukoplakia, crack, wen, blister, or lump in 51 per cent. There was a history of injury in 23 per cent.; the average duration of the lesion was 4 years. Ninety-two per cent. of the cases were **operated on** at the Clinic. Regional lymph nodes or salivary glands were not removed in 77 per cent.; metastasis was demonstrated in 61 per cent. of the 22 per cent. in which these glands were removed. Sixty per cent. of those operated on and in whom no metastasis was demonstrated are living and in good condition. Good results were obtained in 6 per cent. of the cases with metastasis and in 78 per cent. of those without metastasis. Broders (Ann. of Surg., Feb., 1921).

On the other hand, in many cases of epithelioma of the face surgical removal results in much deformity, which can often be avoided by the use of other measures, to be mentioned later, although care in applying them should always be exercised lest the disease progress even beyond the aid of surgery. Pronounced cancer of the lip should never be trifled with, for perfect surgical removal still offers about the only prospect of complete relief.

Surgery has done more for persons suffering from this disease than all other methods of treatment combined. It is not right to consider cases hopeless without first making a careful estimate of the grade of malignancy and of all other factors. The writer ascribes great value, in relation to the results to be expected from removal of the growth in the individual case, to Broders's system of *grading the malignancy of tumors* according to the microscopic picture. This is based on the ratio of differentiated to undifferentiated epithelium in the tumor, which is as follows in the several grades: Grade 1, about 3:1; Grade 2, about 1:1; Grade 3, about 1:3; Grade 4, no tendency to cell differentiation. The number of mitotic figures and of cells

with large, deeply staining nucleoli plays an important part in the grading. The more the neoplastic cell tends to differentiate or approach in structure a normal cell, the lower the degree of malignancy. In certain cases in which the condition seems very extensive, there may yet be a chance of cure by complete eradication. On the other hand, Broders's method has foreshadowed recurrence in spite of an apparently complete operation in a number of cases by indicating a higher grade of malignancy than usually exists in the region, and is useful in preventing operation on a certain group of patients for whom treatment is of no avail.

A high percentage of cures is possible upon wide excision of epitheliomas of the head, face and neck at a fairly early stage, as they almost always remain local, in spite of the very rich lymphatic drainage in this region. Epitheliomas of the larynx respond well to operation, but cancers of the thyroid usually do not. Gastric cancer affords good results if dealt with while still confined to a definite area of the stomach and if the degree of malignancy is not high. All gastric ulcers should be thoroughly excised, otherwise an actually malignant condition may be unwittingly allowed to persist. Cancer of the body of the uterus offers a favorable prognosis under surgery, while in cancer of the cervix radium seems almost a specific. Breast cancers, though accessible and usually recognized early, have not given better surgical results than cancers in other regions, probably because of greater malignancy. Chronic cystic mastitis need not always be treated surgically, but every solitary lump in the breast, or any unusual nodule in association with a diffuse mastitis, should be excised immediately for microscopic study. Cancers originating in the kidney, bladder and prostate, if not too highly malignant, do very well after complete surgical removal. Grading of kidney tumors by the cell differentiation permits of quite accurate estimation of the prognosis. One

of the most discouraging problems is the attitude of some family physicians, patients with definite malignant growths coming for surgical treatment after having been under observation by their physicians for a year or more. E. S. Judd (*Jour. Amer. Med. Assoc.*, Jan. 3, 1925).

Much the same can be said in regard to many cases of sarcoma, although the limitations of surgery are more evident here, and, as will be seen later, other measures are of definite value in a certain class of cases. Mention has already been made of the importance of very early surgical treatment in melanotic sarcoma, although, unfortunately, this is frequently resorted to when it is already too late to obtain a successful result, and after fatal metastases have already taken place.

McCosh, in reporting a series of 125 cases of sarcoma, furnished an account of 11 cases of his own thus treated, 5 of which had remained well for over four years. Of 65 cases reported by Kocher, 9 remained well after three years. Reinhardt reports, out of 54 cases treated, 7 well after three years.

The other forms of cancer, the varieties of sarcoma and adenoma, endothelioma, etc., should always be considered first from a surgical standpoint, and other measures adopted only after having excluded the advisability of surgical removal for very good reasons. In all operations on malignant tumors ultimate success depends on the widest possible extirpation of all diseased tissue, and even of apparently healthy tissue, for a distance around the neoplasm, together with all lymphatics, as directed in works on modern surgery; the mere excision of diseased tissue is often worse than useless.

Report from Hochenegg's clinic of the results of surgical interference in 312

cases of cancer of the colon. Exploratory operation was performed in 18 cases, colostomy in 72, and anastomosis in 50. In 172 cases (55 per cent.) a radical operation was done; of these, 28 per cent. survived for 3 years without further metastasis or recurrence; 7 survived for 10 years. Porges (*Deut. Zeit. f. Chir.*, xcxi, 321, 1925).

The writers have classified as inoperable all cancers of the breast when one or more of the following conditions are present: (1) Recurrent diffuse, subcutaneous nodules in the operative field; (2) single fixed recurrences to the chest wall; (3) presence of axillary nodes on the same side with extension well up beneath the clavicle; (4) well-marked fullness in the supraclavicular fossa of the involved side; palpable nodes may not be present, but they invariably develop later; (5) involved nodes in the opposite axilla; (6) evidence of involvement of the opposite breast; (7) intrathoracic metastases; (8) any recurrences following operation on an inflammatory carcinoma of the breast; (9) metastases to bone; (10) metastases to distant organs. B. J. Lee and N. E. Tannenbaum (*Jour. Amer. Med. Assoc.*, Jan. 23, 1926).

**Associated Surgical Measures.**—It is well known that to obtain the maximum effect from the X-ray it is necessary that the ultimate degree of anemia of the tissue should be obtained. This is accomplished by the roentgenologist by pressure, so that the area treated is rendered as bloodless as possible. Based upon this fact, as well as with the idea of starving of the cancer tissue, Bainbridge and others have attempted **ligation of the blood-supply** in tumors of the face; according to Bainbridge and our own experience, in no case was there a cure, but there did take place an amelioration of symptoms, especially when both external carotids were ligated. A large, fungoid, foul tongue became smaller and less

foul; the large crater-like ulcer in the cheek became smaller; the pain also almost entirely disappeared. Danger from hemorrhage became minimal. The X-ray seemed to have more effect.

At the same time as **ligation of the external carotid** is being carried out, the cervical fascia should be excised.

**Ligation of the internal iliacs** in cancer of the uterus may be performed.

For the last-named lesion, Percy has developed a **cautery** used at a low heat which destroys the cancer tissue. To perform this operation properly it is necessary to open the abdomen so that the hand inserted posterior to the uterus can regulate the depth of heat penetration. At the same time both the internal iliacs are ligated.

As to short-circuiting operations, in cancer of the upper gastrointestinal tract above the stomach, it is frequently necessary to do a **gastrostomy**; in cancer of the pylorus, a **gastroenterostomy**; in cancer of the bowel, an **enteroenterostomy**, and in cancer of the rectum, a **colostomy**. These operations render further treatment with other means more hopeful because they prevent irritating secretions from coming in contact with the cancer area. Since irritation itself is in many instances the cause of cancer, one can see how necessary it is to remove or lessen any irritation which is apt to have an ill influence on the growth.

In many instances operations of the above character may be life-saving, and they should not be neglected.

**II. Non-surgical Treatment.**—This includes all other measures which have been recommended on good authority, either for combating the supposed constitutional conditions underlying the

activity of neoplasms or for directly attacking or influencing the latter.

It should be the object of the medical attendant upon a cancer patient to place the latter in as favorable a relationship with the surroundings as is possible. All sources of worry should be removed. For this reason, it seems not only cruel but unscientific to tell a cancer patient the whole of the evil prognosis, unless, as may happen, it becomes necessary because of familial or other reasons for him to be informed of the seriousness of his condition. In fact, it is best for the patient to be unaware that he is suffering from cancer. The knowledge of his disease will come to him gradually from many sources. All financial and other responsibilities should be removed.

The general health should be improved. Functional disorders should be remedied. The gastrointestinal, circulatory and genitourinary tract should be carefully investigated and all defects corrected.

Non-surgical measures may be considered under the following heads: 1, Diet and hygiene; 2, drugs and chemical agents; 3, caustics; 4, certain physical agents; 5, serotherapy.

**1. Diet and Hygiene.**—These cannot cure cancer, but are features never to be overlooked in the management of the disease. As an example, alcohol, certainly in excess, is most prejudicial in all forms of cancer, as is also stimulating diet of any kind; the harm from the use of tobacco in cancer of the lip and buccal cavity is well known. In most cases at all severe, a carefully regulated and perfectly digestible diet contributes much to comfort and well-being, and should be controlled by the constant care of the physician.

A number of observers have reported the great benefit from an absolutely vegetarian diet, and in some instances have even claimed cures in advanced cases. The relative freedom from cancer of natives in the Far East, many of whom are strict vegetarians and never touch animal food, would seem to corroborate the value of such a diet. Yet, it is very necessary that the patient's resistance be maintained by a full and ample supply of foods. Under no circumstances should loss of weight be viewed with equanimity by the attending practitioner. It is always a sign of ill omen.

Hygiene may also play a more or less beneficial part, especially in severe cases, certainly in mitigating some of the distressing features of the disease. Advanced cases are too often left relatively uncared for, whereas due attention in regard to sunlight and fresh air, and proper cleanliness with antiseptics, may do much to minimize the offensiveness and distress caused by the activity of micro-organisms on the diseased tissue.

Report of successful experiments in the **dietetic treatment** of malignant disease in which substances in the diet promoting growth were all carefully excluded, and others added which tend to inhibit growth. On ordinary food 100 per cent. of the tumor grafts took, some growing to be larger than the body of the mouse. Given the restricted diet 10 days beforehand, none of the grafts took or grew only feebly. Tumors already established, up to 2 or 2.5 cm. in diameter, became arrested and were finally reabsorbed. Large tumors softened and decayed to a friable mass. The growth-promoting substances are certain vitamins, certain internal secretions, and certain chemical substances. The antiscorvy vitamin, and nuclein and phosphorus com-

pounds were carefully excluded, and food denatured by heating to 125 or 130° C. E. Centanni (*Riforma Medica*, Aug. 10, 1918).

The writer collected from the literature 302 cases in which either temporary or permanent recession of a malignant tumor occurred. The causes of recession most frequently found in the series were heat and an incomplete operation. The heat may either be artificially supplied, or the result of an acute febrile infection, such as erysipelas, tuberculosis, or pneumonia. Nutritional factors, and in a few cases, fibrosis, are described as the cause of the absorption. The knowledge that spontaneous regression does occur offers some hope that the cancer research worker may in time find some method of inducing it. G. L. Rohdenburg (*Jour. Cancer Research*, Apr., 1918).

## 2. Drugs and Chemical Agents.—

While no medicines can cure cancer, a carefully directed eliminant and tonic course certainly helps the patient to bear the malady. Many have reported the arrest of lymphosarcoma by the proper, free employment of **arsenic** internally, and **thyroid gland** has been favorably reported on in carcinoma (see vol. i, *ANIMAL EXTRACTS*); also the use of **methylene blue**. It is needless to say that the many advertised quack remedies are worthless, and in all attempts to reach the disease by other than radical surgical operation great care should be exercised lest precious time be lost in which this latter might yield a successful result.

**Hydrated magnesia and magnesium silicate**—0.20 to 0.25 Gm. (3 to 4 grains) of each in a cachet twice daily—prescribed first in a case of papilloma, then in cases of epithelioma in conjunction with **arsenic pastes** locally, and finally in cases of inoperable cancer. In papillomas and superficial epitheliomas perfect results were obtained. In inoperable

cancers the effects were arrest and even reduction of the tumors, marked diminution of pain, and improvement of the general condition. The author now gives the magnesia and magnesium silicate cachets in all operated cases of cancer, with the aim of preventing recurrence. They are taken only 5 days in every 10 to obviate habituation. J. Regnault (*Bull. de l'Acad. de méd.*, July 9, 1918).

Improvement in malignant disease reported under systematic deep intramuscular injections of small doses of **quinine** well diluted, according to Castaigne's technique. The cancer loses its distressing features, and the patient is greatly relieved and possibly buoyed up for months with an illusion of recovery. V. Delfino (*Vida Nueva*, Havana, Aug., 1918).

From investigations of the chemical make-up of cancerous tissue, the writer has been led to consider certain elements as antagonistic to cancer development, *viz.*, silicon, magnesium, calcium, phosphorus, and iron, while others take part in its growth, *viz.*, chlorine, sodium, and potassium. He found that there is a tendency for cancer to fix magnesium, calcium, and especially silicon. In the tumors he studied there were strongly marked deposits of fibrous tissue, of which silica is known to be the chief mineral constituent. He advises ingestion of salts containing silica to assist in the development of defensive connective tissue against cancer. He administers 5 Gm. (75 grains) each of **sodium and potassium silicate** and 10 Gm. (150 grains) of **magnesium silicate** during lunch and dinner. Albert Robin (*Bull. de l'Acad. de méd.*, Jan. 31, 1922).

Administration of **phosphates** and **magnesium salts** recommended, loss of such salts being supposed a factor predisposing to cancer. L. Dieulafoy (*Paris méd.*, Jan. 14, 1922).

Certain measures advocated as indispensable adjuvants to excision or radiation, *viz.*, **sun baths** and **air baths**, **diathermy** and **venesection**. Their purpose is to produce an infiltration of blood cells, especially lymphocytes,

about the growth or the site from which it has been removed, thus enhancing the local immunity and hindering recurrence. Having applied these principles for 13 years, the author reports a persisting cure in 32 out of 44 operated cases, including 11 with an interval exceeding 5 years. Theilhaber (Arch. f. Gyn., Apr. 16, 1923).

Of 3417 cases treated with **carcino-lysin** in Japan, 64 per cent. were benefited, including 26 to 35 per cent. clinically cured. The drug is a ferment prepared from a Chinese variety of pine. Series of at least 30 subcutaneous or intramuscular injections are given, usually in doses of 1 c.c. (16 minims) twice daily, though at first 3 c.c. (48 minims) may be used and the amount then reduced. Matsushita (Deut. med. Woch., Jan. 4, 1924).

Marked improvement from **carcino-lysin** in 1 case of metastases following breast removal; over 50 injections were given in 3 months. The drug causes a general febrile reaction and a local reaction featured by pain in the region of the tumor, with reddening, softening and sometimes disappearance of the growth. Its exact value is not known, as it has been used only as a last resort. F. Blumenthal (Deut. med. Woch., Feb. 29, 1924).

Striking relief from pain, coffee ground vomiting, insomnia, etc., may result from oral use of **liquor potassæ**, given thus:

**R** *Liq. potass. hy-*  
*drox.* .....  $\text{m}\text{xv}$  (1 c.c.);  
*Potassii nitratis.* gr.  $\text{x}$  (0.6 Gm.);  
*Aq. mentha pip.*,  
 q.s. ad .....  $\text{f}\text{3ss}$  (15 c.c.).—M.

The dosage is  $\frac{1}{2}$  dram (2 c.c.) 3 times daily. From the 1st dose, patients sleepless for several nights slept 14 hours continuously, vomiting ceased and small nodules disappeared, while in 2 cases the tumor mass was greatly reduced in size. A possible specific effect on cancerous growths is discussed. D. M. Gall (Lancet, May 31, 1924).

The use of **sodium bicarbonate** is based on the following facts: 1. That

cancer is nearly always found in areas where normal secretions are acid. 2. That both animal and plant tumors grow only in an acid medium (generally lactic acid). 3. That the blood returning from a tumor area contained more lactic acid than blood returning from a homologous non-tumor area (Cori). 4. That Doub and others working with the X-ray found that it produced not only a localized increased alkalinity in the tissues directly treated, but a generalized alkalosis over the entire body. Thus, the attempt to produce an increased alkalinity of the host by ingestion of sodium bicarbonate would seem to be of value. As much as 1 dram (4 Gm.) 3 times a day may be given. At first the patient is likely to complain of nausea and loss of appetite, but if the medication is continued, this indisposition disappears and the patient enters upon a period of increased well-being.

Sodium bicarbonate in the form of a 10 per cent. solution may also be used as a local dressing over ulcerating growths. At first it causes marked edema and swelling, but this quickly disappears. The foul discharges are controlled by the treatment, and the tumor becomes smaller.

**Chemical Agents.**—Czerny and Caan made extensive trials with **salvarsan**, and concluded that a therapeutic trial of it is indicated in all inoperable malignant tumors with a positive Wassermann reaction, especially in sarcomas. It has a marked effect in lessening pain. In operable sarcomas, if a positive Wassermann reaction is present, a preceding trial of salvarsan might be made. In cachectic and weakened individuals it is contraindicated. Hutchinson has pointed out that arsenic has a tendency to produce cancer, notably

epithelioma, and advocates its use only in cases which very specially demand it.

Attracting attention in connection with the chemotherapy of cancer has been the frequently successful treatment of mouse tumors by intravenous injections of **tellurium** and **selenium** in a solution of eosin as vehicle. Wassermann (Berl. klin. Woch., xlix, 4, 1912) published striking results on mouse tumors by using these metals. Their sodium salts become reduced by cancer cells, and their oxides are deposited within the cancer cells as a black or red powder. A 1 per cent. solution of these salts injected into the tumor will cause it to soften and break down. Injected intravenously the salts alone cannot do this, but in combination with eosin the diffusion of the metals into the cancer cells is rapidly facilitated, and with just the right preparation Wassermann was able to accomplish a cure of a number of mice tumors. By the seventh or eighth daily injection complete healing had occurred. The exact preparation of the remedy, however, has been a matter of very great difficulty. The dose must approximate the fatal toxic dose of the remedy. Unless all the tumor is destroyed recurrence always results in 8 to 14 days, and when recurrence has set in the tumor is refractory to treatment. The destruction of the tumor cells is marked in particular by an effect on the nucleus, which he described as a pyknosis. Before the cell body disappears the nucleus is broken up and extruded. No leucocytic infiltration occurs on the border of the tumor. No organs seem to suffer from the toxic effects of the remedy except the liver and spleen, the latter showing a lymphatic transformation, and the former, a forma-

tion of small collections of lymph-cells at the division points of the portal veins.

C. E. Walker gave **selenium** in a series of cases one of which he reports at length. The patient was a woman of 60 years who had been operated upon 15 years before for cancer of the breast. At the time of examination she was cachectic and the liver was enlarged and evidently the seat of a secondary growth. Treatment was begun July 27, 1910, with a milligram ( $\frac{1}{100}$  grain) of selenium oxide ( $\text{SeO}_2$ ) three times a day. By September 2d there had been a gain in weight of  $2\frac{1}{2}$  pounds and the liver dullness had receded two finger-breadths. During the treatment the patient at times gave evidence of renal irritation. The improvement in the general condition was, however, continuous, and 18 months after the beginning of treatment there had been no relapse. E. G. Kessler (N. Y. Med. Monats., Jan., 1912).

The injection of **colloidal selenium** has established a definite claim for consideration in certain cases. In a class of patients whose outlook has till recently been almost hopeless, considerable benefit may be expected. Pain, sleeplessness, ulceration, and discharge are markedly diminished. In favorable cases a fair degree of comfort is attained, several cases returning to work. In a few, the relief comes within measurable distance of a cure. E. Watson-Williams (Brit. Jour. Surg., July, 1920).

Prof. Albert Robin (Bull. de l'Acad. de méd., 9-10, 1920) believes that the specific exciters for cancer cell growth are amino-acids and result from irregular metabolism. Their formation is in the nature of an enzyme action. Sulphur in the body, and sulphur metabolism are not disturbed. He recommends **sulphur** in a highly organized form in the treatment.

W. Blair Bell (Lancet, Feb. 9, 1924) has reported 122 cases treated with col-



**colloidal lead iodide** preparations, usually administered intravenously. Little specific information on the mode of preparation or dosage is given. The patients usually complain of pain in the tumor in 2 to 8 hours after injection. Local redness may be noted. In favorable cases the mass seems to break up into separate smaller tumors. At this juncture the cases should be subjected to the X-rays. Sarcomas may soften, liquefy and be absorbed. Among the patients treated there was not a single early case. In most, the outlook was hopeless. Of the 122 cases treated between Nov. 9, 1920, and Nov. 9, 1923, there were 19 alive and believed cured on Dec. 21, 1923; 12 were arrested or improving, 12 had improved but later died, 30 had been unimproved, and most of the remainder had died from various causes or discontinued treatment. The treatment is deemed advisable in inoperable cases and to prevent recurrence in operated cases. In a later paper, with W. R. Williams and L. Cunningham (Lancet, Oct. 17, 1925), Bell stated that 58 later cases had been treated almost entirely by intravenous injections of **colloidal metallic lead**. Again, Bell (Lancet, Mar. 13, 1926), having treated 227 patients with lead, states his belief that all types of malignant growths are probably amenable to the beneficial influence of lead, provided it can reach the tumor cells in sufficient quantity. Adjuvant surgical and radiologic measures in suitable circumstances are useful. When the growth has been partly, or apparently entirely, removed, intravenous injections of lead should be given within a few days of the operation when possible. The lead treatment is difficult and to some extent dangerous, and can be employed safely only

by those thoroughly experienced in the work and having laboratory facilities at their disposal.

**Organotherapy.**—Another form of treatment of cancer is that by organ extracts. Among the earlier trials were those of **thymus extract**. F. Gwyer (Ann. of Surg., xlvii, 506, 1908) reported 16 cases treated in this manner. He obtained a temporary improvement in 10 cases and no result in 6. The *rationale* of this form of treatment depends upon the rarity of cancer in the young and the functional activity of the thymus at this period.

Rohdenburg, Bullock and Johnston (Arch. of Int. Med., Apr., 1911) reported treatment of inoperable cases with **thymus gland** alone and in various combinations. In almost all, nutrition was markedly improved and the pain was greatly diminished. The discharge and bleeding were stopped or lessened. The glands diminished in size and in some cases disappeared, and the tumors themselves showed a cessation of growth and in some cases a temporary decrease in size. The 48 cases observed led to the conclusion that thymus extract, given for 3 to 5 weeks, markedly influences malignant tumors. After this comes a period of quiet for about 2 weeks, after which the tumor either gradually increases in size or remains for a long period stationary, or, rarely, disappears altogether.

**Pluriglandular therapy** when it includes **thyroid** and **sexual glands** induces in a cancerous growth a retrogressive change. In some it checks the active growth of the tumor, and in a limited number causes its apparent disappearance. H. N. Das (Calcutta Med. Jour., Nov., 1917).

**Thymus extract** seems to destroy cancer cells *in vitro*, even when greatly

diluted. The best results have been obtained with fresh, unheated thymus extract. The writer's patients bore daily injections of 10 c.c. (2½ drams) without signs of intolerance, general or local reaction, or anaphylaxis. S. Nordentoft (Ugeskr. f. Læger, Jan. 23, 1919).

**Epinephrin (adrenalin)** in 1:1000 solution, painted or swabbed over the surface of the growth, relieves pain, arrests hemorrhage, and even tends, by causing constriction of the vessels, to cause partial retrogression of the growth. Injections of 10 minims of the same solution into the tumors enhance further the latter effect; but the injections should be administered under strict asepsis, and after carefully treating the surface with a solution of hydrogen peroxide.

[The local effects of **adrenalin** in this connection were observed by C. Piessinger, who attributed them to its effect on vessels of the neoplasm. In cancer of the rectum, he found that painting twice daily with 30 to 100 drops of a 1:1000 solution of adrenalin in a tablespoonful of water decreased the proctitis, checked the discharge, and brought about a temporary diminution of the growth. Mahn had previously obtained prompt results by simply painting the growth with the 1:1000 solution. The neoplasm partially retrogressed, then remained stationary, free from pain or hemorrhage, the patient being in apparently perfect health. In 4 other cases the results were also satisfactory. Berdier and Falabert tried injections in advanced cases and found that they caused diminution of the tumor and of the adjoining glands, abolishing pain and increasing the patient's weight. The injections were made into the tumor, or, when this was inaccessible, into the arm, or over the organ involved. J. E. Rhodes reported a case of inoperable nasopharyngeal sarcoma in which the injection of adrenalin into the growth, together with local swabbing and spraying, caused marked reduction in size and alleviated the pain, though the patient's life was not prolonged. J. Price-

Brown also found that adrenalin checked the circulation in sarcoma and lessened bleeding. Reicher found that adrenalin injected around an experimental tumor in mice almost invariably led to its subsidence. From 2 to 13 injections accomplished this in rats.—Ed.]

Desiccated **adrenal gland** is of advantage in these cases to prevent anemia by supplying the blood with the oxidizing constituent of the hemoglobin. Three grains three times daily with **iron**, preferably Bland's pill, one grain, prolong life by counteracting the progress of the cancerous cachexia.

[The usefulness of adrenal gland in this connection was illustrated by one of Dr. Sajous's cases of advanced uterine cancer in which life was considerably prolonged, improvement of the patient's condition having become manifest soon after the use of the gland had been begun. It seemed also to prevent severe pain, doubtless by causing constriction of the arterioles, thus reducing the local hyperemia and swelling. The patient died, in fact, without knowing that she had suffered from cancer.—Ed.]

Report of 2 cases of epithelioma at the root of the nose, both in women 80 years old, in one instance of 1 year and in the other of 10 years' standing, which healed under 0.4 to 0.6 Gm. (6 to 9 grains) of **thyroidin** and 3 Gm. (45 grains) of **ovarin** daily, divided into 2 doses, before meals. Healing took place in 6 and 5 months, respectively. Pathologic examination of the lesions, with a diagnosis of epithelioma, is stated to have been made by C. Nicolle, of the Institut Pasteur of Tunis. In a case of anorectal cancer with metastases in a woman of 83, administration of **extract of bile**, **thyroidin**, and **pancreatin** was followed by marked symptomatic and general improvement for about two months. Naamé (Gaz. des hôp., Feb. 5, 1921).

**Pituitrin** used in a case of severe hemorrhage from an extensive inoperable epithelioma of the tongue, 1 c.c. (16 minims) being injected into the tongue muscle. All bleeding immediately stopped, and in addition

the glands decreased in size and the patient gained in weight, though dying 9 months later. Injections were thereupon given in 36 inoperable cases, most of them experiencing pain in the back or abdomen and a sense of constriction in the growth. The single dose never exceeded 3 c.c. (48 minims). In all cases improvement and delay in the onset of secondary glandular enlargement was observed. J. H. Norgate (Brit. Jour. of Surg., Apr., 1922).

The simultaneous use of **radium**, **thyroid gland**, and **adrenal gland**, the two latter in the above-mentioned doses, improves the likelihood of recovery beyond that afforded by radium alone.

(See article on Animal Extracts in vol. i, for additional data on the treatment of cancer by organotherapy.)

**Local Destructives.**—In earlier years, previous to the better knowledge of metastasis, the advances of modern surgery, and the employment of the X-ray, etc., there was much use of destructive methods, in hopes of totally removing neoplasms and replacing them by healthy scar-tissue. It may be said that these have gradually been employed less and less by the medical profession, although they are still a great field of enterprise for advertising quacks. While they have their value in certain rare instances, it is doubtful if, as often used, they do not do more harm than good. A striking illustration of this is found in the use of nitrate of silver, with which it was formerly so common to "touch up" rebellious sores; by this means innumerable instances of mild epithelioma were goaded into lesions of most serious character, beyond hope of relief by any means; this is especially true of the disease within the mouth or on the face.

Caustics have also been employed in

carcinoma in many deeply seated locations, often with disastrous consequences, resulting not only often in death from exhaustion, but also in the disease recurring *in situ*, and in metastases which could not be thus reached.

Occasionally, caustics of various kinds, if used just rightly, in proper cases, may eradicate the disease. The principle to be applied is that they must be radical, destroying deeply and thoroughly, even to some distance beyond the diseased tissue; if there are already metastases, however, the ultimate result must be unfavorable. Space does not permit enlarging on this subject or giving details of treatment, but an illustration of what is intended is found in the use of the well-known **Marsden paste** of arsenious acid in certain cases of epithelioma. When rightly handled this cures many cases permanently, leaving satisfactory scars; the same is more or less true of **caustic potash**, **Canquoin's paste**, **Bougard's paste**, and perhaps others.

Jennings, of London, in his book on "Cancer and Its Complications," states that "when caustics are employed to destroy a cancerous growth of any considerable dimensions the results are far inferior to excision or amputation under modern conditions. The bulk of the growth is hardly ever eradicated, and manifest local recurrence occurs ordinarily after the lapse of a few weeks. The caustics are applied and reapplied, and this sad treatment goes on until the patient is relieved by death of a treatment which adds pain to that of the disease, which it ordinarily aggravates."

He makes an exception in favor of caustics in certain very old and debilitated patients where there is an open ulcer, with the surrounding tissues adherent to the ribs, for the purpose of arresting offensive discharges

for a while. He recommends a preparation consisting of:—

**R** *Cocaine hydrochloride* ... 2 Gm. (30 grs.).  
*Caustic potash* 6 Gm. (1½ drs.).  
*Vaseline* ..... 8 Gm. (2 drs.).

After the skin is well cleansed, small portions of this paste are well rubbed in with a wooden spatula, and in a few minutes considerable tissue can be destroyed. The charred portions should be carefully wiped away with absorbent cotton during the application. Albert Carson (Mass. Med. Jour., Dec., 1911).

Following salve recommended for epithelioma of the skin: 0.2 Gm. (3 grains) each of **arsenic trioxide**, **copper sulphate**, **methylene blue**, and **methyl violet**; 0.5 (7½ grains) **quinine hydrochloride**; 0.75 Gm. (12 grains) **tartar emetic**, and 1 Gm. (15 grains) each of **camphor**, **menthol**, **phenol**, and **antipyrin**. The last 4 ingredients, mixed together, deliquesce and form the vehicle for the other ingredients added in turn, leaving the methylene blue and methyl violet till the last. Two applications a week are made. De Rezende (Brazil Medico, May 11, 1918).

But most of the cases to which this form of treatment is suitable yield to **X-rays** or **radium** (*vide infra*), and with much less deformity.

**Liquid air** and **carbon dioxide snow** may also be employed with advantage in proper cases and leave a very slight scar; the latter is much more readily handled and controlled.

**Curettage** has been strongly advocated in the past, and may occasionally be of value in removing superfluous diseased tissue, in conjunction with other treatment. But used alone it is seldom able to reach and remove all the morbid growth, and many recommend the subsequent use of caustics, or the free employment of the **galvanic cautery** after curettage. In

small, superficial epitheliomata, however, a thorough curetting, with the subsequent filling of the cavity with powdered **pyrogallic acid**, will often give useful results.

**Medical Applications.**—These, of course, can have very little curative effect on any of the forms of cancer, but it is a mistake not to appreciate their value as adjuvants, and to use them properly under certain circumstances. Mild **ichthyol ointment** is of great service in connection with the **X-ray** treatment of epithelioma, and various antiseptic and soothing applications, in the form of lotions or ointments, will often add greatly to comfort and aid the healing process.

**Peroxide of hydrogen**, followed by a proper ointment, is invaluable in many ulcerating forms of cancer, where foreign micro-organisms contribute so largely to the keeping up of the production of pus.

The much vaunted treatment of carcinoma by **trypsin** is, perhaps, worthy of mention. James Beard, of Edinburgh, called attention to the fact that about the seventh week in fetal development the villi of the chorion begin to disappear, synchronously with the development of the pancreas, and he assumed a connection between the two events. He further assumed that all malignant tumors represented abortive attempts of certain cells to reproduce the chorionic type of cell, and that those cells which do this are misplaced and included in other tissues during embryonal development. The correlation of these two assumptions furnished the explanation of the action of trypsin in cancer. He then found by actual experiment that trypsin possessed a specific and destructive effect on chorionic cells. Further investigations led to the conclusion that trypsin quickly dissolves cancer cells, while pepsin attacks them with difficulty. Cancer cells produce an intercellular ferment capable of dissolving all tissues; this ferment is neutralized by trypsin.

Unfortunately, the high hopes to which these investigations led were not confirmed by other observers, and, while some favorable results were reported, wide experience has shown that but little if anything can be expected from this treatment.

**X-ray.**—Most observers are now pretty well agreed upon the field of usefulness of the X-ray, though some are still extravagant in their claims as to its value.

The X-ray used in the treatment of cancer is of two types: the **low voltage** and the **high voltage** (above 200,000 volts). The former is satisfactory in the treatment of superficial lesions, but has been proven of little value in the treatment of deeper organs. Wintz, of Erlangen, has been the most active sponsor of the **deep X-ray therapy**. His results have been marvelous, especially in the treatment of *sarcoma*. Deep therapy gives results which cannot be obtained by any other method. The long dosage given by the earlier users of this method induced the so-called X-ray sickness, which Doub, of Detroit, has conclusively shown to be due to an increased alkalinity of the tissues and which is counteracted by the use of calcium lactate.

The high voltage, *i.e.*, the so-called deep therapy, should not be used directly over the heart and lungs, because of its destructive action upon the blood cells and the fibrosis of the lungs which it causes. Lee warns against intensive treatment for advanced cases, because it may do more harm than good. Lee also believes that high voltage therapy has a limited field in the treatment of recurrent and metastatic mammary cancer. Lee and Tannenbaum (Jour. Amer. Med. Assoc., Jan. 23, 1926). The post-operative treatment should not be started for 2 to 4 weeks after operation or until the patient has recovered

completely from it. Before a case is treated for recurrent carcinoma the chest should be examined by the Roentgen ray to determine the presence of metastases. All suspicious bone pains also merit consideration, and if metastases are found, further Roentgen therapy is useless.

According to W. A. O'Brien (Jour. of Cancer Research, Sept., 1925), it seems to be indicated that the usual doses of the X-rays do not directly kill the cancer cells, but first stimulate defensive reactions in the tissues. From the practical standpoint, **pre-operative radiation** has a scientific basis in treating cutaneous neoplasms. Carter Wood (Jour. Amer. Med. Assoc., Oct. 3, 1925) states that he cannot see that the effect of radiation on a tumor is anything primarily but a direct effect on the cells. If 4 platinum needles of 1 mg. each are inserted in a square in an animal or a human tumor at a distance of 1 cm. apart, the tumor tissue between these needles will necrose after from 90 to 100 mg. hours. The tumor tissue outside the needles requires 700 mg. hours. The reason for this is that the vessels nourishing the interior of the square are thrombosed while the blood-supply to the cells outside the square is unimpaired. Jüngling (Fortsch. a. d. Geb. d. Roentgenstr., xxx, 101, 1922) agrees that the action of the X-ray on cancer is purely local. Wintz states that the connective tissue merely replaces the cancer cells which are destroyed. James Ewing states that no form of radiation yields any success in debilitated or cachectic subjects.

In using the X-ray, periods of freedom from treatment must be allowed in order that the organism may develop either a resistance to the poisonous products of disintegration or a means of

destroying or extruding them. In the gastrointestinal tract, following X-ray therapy, the broken-down products may be absorbed and produce toxic manifestations just as when the poisonous material is absorbed directly from the tumor into the tissues through the blood and lymph vessels. The same applies to the skin, the uterus, and the respiratory and genitourinary tracts.

It must be remembered that the X-ray is a double-edged tool, which, while capable of effecting very great good, is also capable of inflicting harm, both to the patient and the operator. But this latter need not at all deter one from using it when it is rightly indicated, for, while there have been a few sad examples of serious damage to the operator, these took place mainly before the dangers were fully appreciated, and on the other hand there are thousands of operators who have manipulated it daily for years without harm. Also in regard to any harm to the patient, there is practically no danger with a careful and skilled operator. Success in the use of the X-ray depends, indeed, very largely upon the knowledge, experience, and care of the operator; it is not enough simply to apply the X-ray; it must be rightly employed to be effective.

Warning against over-radiation. This produces changes in the connective tissues, with a diminished blood-supply, so that an area of reduced resistance is produced in which the cancer cells grow with great activity. Recurrences after prophylactic radiation are very difficult to eradicate. Recurrences occurred more frequently after postoperative radiation of tissue than in those subjected to surgery alone. Postoperative radiation of proper dosage will produce a local resistance to cancer cells. Report of 2 cases in which the irradiated areas

remained free of recurrences, but carcinomatous nodules developed in the unexposed skin between the areas treated. W. A. Evans and T. Leucutia (Amer. Jour. of Roentg., May, 1925).

The treatment by X-ray finds a promising field of operation in the superficial, basilar-cell epithelioma about the face, and in this the results are commonly most gratifying, the lesion melting away and often leaving a hardly perceptible scar. Pusey has reported 72 per cent. of successful cases remaining well after a period of three years or more, and the experience of many others confirms this; indeed, in properly selected cases, when judiciously used, this method of treatment can give even a much larger percentage of cures.

Many have reported that the X-ray is of value in connection with the surgical removal of cancer, and that its postoperative use will prevent the recurrence of the disease. In recurrent and non-operable cancer the proper employment of the X-ray is often of service in relieving pain and in improving the condition of the ulceration, and it has been claimed by good observers that in the latter instances the disease has been checked.

In *operable* cases of *breast cancer* the writer recommends an *ante-operative* course of X-ray treatment over the breast, axilla, and supraclavicular region, as much radiation as possible being given within a period of 1 or 2 weeks. **Radical operation** should be done within a few days, and soon after (within 3 or 4 weeks after the first X-ray treatment) a second course of radiation given to the limit of skin tolerance, the whole process being completed within 2 months in an early or average case. At least 3 areas should be treated: the mammary region, the supraclavicular, and the scapular and posterior axillary. He

employs the radiation from a Coolidge tube filtered through 6 mm. of glass or aluminum, with 5 milliamperes of current. With a focal skin distance of 30 cm. an exposure of 20 minutes is given; if 40 cm., 35 minutes. Each area is covered within 2 weeks.

In *inoperable* cases **radium** is used in addition. Two weeks after exposure to the **X-rays**, steel needles, containing 10 mg. of radium each, are placed, under aseptic precautions, throughout the tumor at distances of 1.5 cm., if the treatment is to last for 8 hours, or 2 cm. if for 16 hours. The tumor then usually disappears or shrinks so that operation is possible. In recurrent carcinoma the same procedure is used. If the disease is localized to the area treated, good results may be expected. G. E. Pfahler (Amer. Jour. of Roentg., Nov., 1921).

The highly penetrating **X-rays** have advantages over radium even for external application. Following a single irradiation, ulcerating recurrent breast cancers healed over and nodules disappeared. Lameness from metastatic involvement of the pelvic bones subsided so that bedridden patients were enabled to walk again. Persons with pancreatic cancer regained their appetite, strength and weight, and several returned to work. In a number of cases distressing urinary symptoms attending cancer in the pelvic organs, not only uterine, but prostatic, rectal, and vesical malignancies, showed abatement. J. T. Case (Jour. Mich. State Med. Soc., Jan., 1922).

Palliative **X-ray** treatment in advanced, inoperable, cachectic, hopeless cases of cancer, primary or recurrent, advocated on the basis of cases described. Fractional doses applied at intervals were used, with marked relief to the patients. Among the cases cited is 1 of a man aged 70, with gastric cancer and metastases in the mediastinum. Three erythema doses were given at 14-day intervals over the stomach region, without cross-fire. A year later the patient had no symptoms. Leddy and Weather-

wax (Amer. Jour. of Roentg., May, 1924).

Most observers agree that the X-ray should not be used in cancer of the lower lip, tongue, or throat; nor in cancer of the breast or penis; the reason probably is that the blood-supply is so excessive that the operation of the ray is interfered with, for we know that in the use of the Finsen light in the treatment of lupus the part must be kept exsanguinated by constant pressure with the lens.

The treatment of a cancer should not be forced for, as Opitz says, a dangerous and possibly stormy reaction may occur. Opitz states that in two instances in man and frequently in animals, he has observed death intervene during the rapid retrogression of a sarcoma. Jüngling (Roentgenbehandlung Chirurgischer Krankheiten) states that radiation of primary melanotic tumors is absolutely contraindicated. Unfavorable for radiotherapy are: Carcinoma of the tongue, mouth, or tonsils; bronchiogenic carcinoma. Herman Johnson (Brit. Med. Jour., ii. 570, 1922) believes that graded X-ray treatment raises the body resistance. In cancer of the breast cases, divided doses are probably best. The massive dose is best in uterine carcinoma. Cancer of the cervix is better excised. Of skin carcinomata, 84 per cent. were cured by Hazen and Whitmore.

The type of epithelioma giving the best results is the basal cell epithelioma. In the writer's opinion, practically every case of this kind can be cured by the **X-ray** treatment. In certain cases showing extensive tissue change, he prefers to supplement it with methods to remove much of the diseased tissue, such as **electrocoagulation**. Squamous cell epitheliomata are cured with greater difficulty, and a most guarded prognosis

should be given. If for any reason electrocoagulation can not be applied in epitheliomata, preceding the X-ray therapy, excision is indicated. If metastasis has already taken place, the involved glands should be removed surgically.

Degenerating moles should be removed either by **desiccation**, **electrocoagulation** or **excision**. The writer prefers desiccation or electrocoagulation. The necessity for wide excision and complete removal is urged. Following the removal, a single full dose of deep röntgentherapy should be given, and usually this is sufficient. G. E. Pfahler (Jour. Amer. Med. Assoc., lxi, 985, 1917).

In nevocarcinoma or melanosarcoma, starting in imprudently irritated nevi or beauty spots, dangerous through lymphatic and visceral metastases, and met with even in young subjects, X-ray treatment is useless and should be replaced by **surgery** or **electrolysis**. Small skin tumors secondary to cancer, *e.g.*, of the breast, frequently disappear under the rays, but the prognosis of the underlying disease is not in the least improved. In all skin cancers an early diagnosis of the type of cell present, basocellular or spinocellular, should be made, by histological examination if necessary, and the treatment at once adjusted accordingly. J. Darier (Bull. de l'Acad. de méd., June 4, 1918).

In the treatment of cases of *recurrent breast cancer* with heavily filtered rays, the rapidity with which palpable and perceptible lesions in frankly inoperable types disappeared seemed highly encouraging. The method proved relatively free from hazard, pain, and prolonged invalidism. The method is superior to any other treatment for extramammary adenopathy. The average exposure in the author's later cases was 1½ hours per day of active treatment. E. A. Merritt (Jour. of Radiol., Sept., 1922).

What has been termed the "carcinoma dose" of the X-ray is merely the maximal, and not the optimal dose of the ray. Whereas cancer recurred

in those of the cases treated with this maximal dose, most of the apparently cured cases had received small doses. The ray does not directly destroy the cancer cells, but causes the formation of chemical substances antagonistic to them and which may influence them even if the ray is not applied directly over the growth. Direct destruction of the cancer cells could not be effected without harming the surrounding normal tissues. The ray leads to stimulation of the vegetative nervous system, especially the vagi, and its effects resemble those of cholin. E. Opitz (Med. Klin., Sept. 9, 1923).

The X-ray is to be used for widespread radiation, and where the lesion is at a distance from the skin. Many breast cancers can be successfully treated with it alone. The tendency now is to divide the dose. It is indicated for malignant glands; the glandular area in cancer of the cervix, rectum, bladder and prostate; any deep-seated, inaccessible growth unassociated with vital glands, such as the adrenal and pancreas; metastasis to the lungs and bones, and sarcoma. W. II. Schmidt (Amer. Jour. of Roentg., Sept., 1924).

The normal reactions in the healthy tissues about a cancer can be aroused by a considerably smaller dose of radiation than has been customary. Normal cells play an important part in the destruction of cancer cells. The embryonic, undifferentiated cells in a cancer are the dangerous ones and are also the ones that succumb most readily to a mild radiation dose. The dosage factors referred to are 220 kv., 4 ma., 50 cm., and an average time of 3 minutes twice daily for superficial lesions and 10 minutes once or twice daily for deep-seated lesions. Large portals of entry and cross-fire technic are used in order to cover all the surrounding lymphatics. If one can surround the cancer cells with sufficient leukocytes and keep up the supply by a continued body reaction, heavy irradiation dosage is unnecessary. A number of cases successfully treated



by this method are referred to. W. L. Clark, J. D. Morgan and E. J. Asnis (Radiol., Oct., 1924).

The blood should be examined before and after X-ray treatment. Leukopenia reaches its lowest point about 6 days after the beginning of treatment. It lasts for about 9 days, then reaches the pre-treatment level in about 4 weeks. Eosinophilia, 7 to 23 per cent., is usual 2 to 3 weeks after short-wave-length irradiation. Should anemia be present, deep therapy or forced superficial therapy should not be used until the blood is brought up to its normal standard. If necessary, blood transfusion should be carried out. Minot and Swiling found that cases not showing leukopenia after X-ray treatment did better than those that did.

The work of Doub, Bolliger and Hartman (Jour. Amer. Med. Assoc., Oct. 24, 1925) has shown that there is always an increase in the alkalinity of the tissue fluid after long-continued treatment by Roentgen rays. This was proven by the determination of the pH of the plasma and of the urine and by the use of indicators in the tissues. The alkalosis was proved not to be the result of tissue oxidation or the washing out of carbon dioxide by their study of the expired air of patients, collected before and within a two-hour period after irradiation. The best means of protecting a patient against this sickness was found to be the use of calcium lactate, which was given in the form of a 5 per cent. solution, injected intravenously to the amount of 20 to 30 c.c. ( $\frac{3}{8}$  to 1 ounce) immediately following the radiation. Later it was used by mouth; about 4 drams (16 Gm.) were given every half-hour for 4 to 6 doses, and frequently the series repeated. They also refer to the good

effect of morphine, which was given in the dose of  $\frac{1}{2}$  grain (0.03 Gm.) about  $\frac{1}{2}$  to  $\frac{3}{4}$  hour before treatment. This, I believe, should be used in breast and neck cases. The lactate was repeated every hour if the patient showed any signs of recurrence of nausea. These conclusions have been confirmed by Pagniez, Coste and Solomon (C. r. Soc. de biol., Feb. 27, 1925).

Webster (Brit. Med. Jour., xi, 507, 1922) claims that preliminary ionization with copper selenate renders the tumor more sensitive to the X-ray.

Warnekros resorts to blood transfusion to enhance the effects of X-ray local treatment, while Bier injects 30 c.c. (1 ounce) of hog's blood into and around the tumor. Fränkel advises irritative radiation of the thymus. Lymphopenia favors the growth of cancer, and Fischera and Odier found that splenectomy markedly predisposes to cancer. Fränkel noted marked delay in cancer development after inoculation upon addition of splenic extract. The writer, therefore, proposes that destructive radiation of cancer be combined with irritative radiation of the spleen. F. von der Hütten (Strahlenther., Dec. 15, 1921).

For anorexia and weak digestion after radiation treatment, Sansum's expedient of giving pancreatic extract in increasing doses until it becomes effective, after which it can be stopped without loss of the benefit produced, is valuable. The anorexia disappears in 48 hours under this drug. H. J. Ullmann (Radiol., Dec., 1924).

Association of the connective tissue in the healing process has been emphasized by Kok and Vorländer. This Opitz holds to be, however, but an increase in the natural defensive activities of the organism. Advances in treatment may be made when it is definitely determined what element of the tissue is involved in the healing process and what remedies, means or measures may initiate this curative re-

action. It is possible that a remedy acting upon the glands of internal secretion may activate these processes. Opitz, from his experiments on scar tissue and Roentgen exposure, believes that the adrenals are involved, while Resse and Poos have associated the pancreas with such exposure. It is unknown if and to what degree the thymus, thyroid and hypophysis are associated with the curative action of the X-ray.

Opitz mentions remedy No. 67, with which experimentation has been in progress in the Frauenklinik at Freiburg, and with which it has been possible to cause to disappear tumors of the size of a cherry or larger. Previously it had not been feasible to cause these tumors to disappear with any means other than the X-ray. Remedy No. 67 consists of a combination of dyes, extracts of glands of internal secretion, metals and other ingredients. All new remedies must be used upon cancer cases with the greatest care and utmost precaution, since toxic reactions and even fatal poisoning may occur.

The prevailing custom of regarding cancer as cured after an interval of freedom of 5 years or more is fallacious, for undoubtedly cancer is a general disease with a localized manifestation. The period of freedom apparently means only that the prior cancer which retrogressed or perhaps disappeared under X-ray or other treatment created an immunity, the duration of which is unknown but evidently depends upon many factors. When this period of immunity has passed, the same factors which led to the production of the original cancer will cause another cancer to develop. These redeveloped cancers are not recurrences, but are entirely new formations. Thus, when cancer occurs in the scar of former operations after a period of years, the implication is that this is a new growth and not the development of cancer rests in the scar tissue.

Summarizing the results of the **Roentgen ray** treatment of *sarcoma* at the Radium Institute of Paris from 1919 to 1921, Regaud, Roux-Berger, Jolly, Lacassagne, Coutard, Monod and G. Richard (Paris méd., Feb. 2, 1924) found that out of 62 cases treated, 16 were well early in 1923, 6 were alive but had recurrences, and 40 were dead. There were no cures of myeloid or fibroplastic sarcomas. In the absence of a biopsy for pathologic study, the treatment is largely empiric and the prognosis uncertain. Biopsy should be avoided or preceded by X-ray treatment when the growth is not ulcerated.

Whereas surgical treatment is generally ineffective in *lymphomas* and *myelomas*, and may be disastrous, wide Roentgen treatments are very efficient, and a local cure is obtained in the majority of cases. Metastases are very frequent, but they had already started at the time of treatment. In advanced cases, the metastases develop more rapidly upon removal of the principal growth, yet may sometimes be successfully treated. In *ostcogenic* or *chondrogenic sarcomas* the X-ray appears to be the treatment of choice. **Radium** is seldom indicated in sarcoma, the growths usually being too large for radium-puncture, which might, furthermore, lead to dissemination of tumor cells. The *epulis* and *myeloplax* varieties of sarcoma are the chief indications for radium. In *fibroplastic sarcomas*, usually resistant to radiation, **surgical treatment** is that of choice.

Case apparently one of sarcoma of the thigh, with secondary growths in the inguinal region, liver and lung in a man of 50, in which all the tumors disappeared under intensive **deep X-ray therapy**. J. H. Schroeder (Jour. Amer. Med. Assoc., Jan. 6, 1923).

Case of *melanosarcoma* of the forearm measuring 4 x 3 centimeters, with 3 metastases, which was successfully treated with the X-ray, no recurrence being present 3 years later. The tumor received a total of 3½ hours of unfiltered rays during a period of 5 months, and the arm, chest and axilla, 13½ hours of filtered rays during 8 months. A. K. Owen (Amer. Jour. of Roentgenol., Apr., 1924).

Clinical healing obtained in 13 out of 35 cases of *round-cell sarcoma* which had lasted for varying periods up to 6 years and 3 months. In one group of cases, radiation had yielded startling primary results, but recurrences in other parts of the body and anemias proved fatal in almost all the cases. In *lymphosarcomatosis* it is far better to divide a definite amount of irradiation over a period of time, from 1 to 2 weeks, in order that the body dose be as small as possible. Roentgen rays and radium together, with arsenic medication, are the methods of choice in round-cell sarcoma. B. F. Schreiner and C. C. Herger (Radiol., Nov., 1925).

**Radium.**—With this agent some excellent results in a variety of cases, including epithelioma, have been reported.

Wickham's earlier work at the Paris Institute included some remarkable observations in cancer of the breast. By means of metal shields and other coverings he varied the activity of the radium, and for deeper tumors employed only the hard *beta* and the *gamma* rays, which were made to act on the disease for many hours daily. Also, the cross-fire method was developed.

According to Pfahler (Surg., Gyn. and Obst., Oct., 1925), radium is probably more selective in its action on tumor cells than the X-rays. Therefore, when one can choose, it is advisable to use radium whenever it can be brought in direct contact with the malignant disease. The X-rays, however, are pre-

ferable when the radiation must be carried to some depth through other tissues to reach the tumor, or when the disease must be destroyed at a depth of more than 3 centimeters, (1) because the direction of the radiation from radium is most difficult to control, while a beam of X-rays can be directed almost like a bullet or knife; (2) because the radiation from radium, like that of the X-rays, diminishes with the square of the distance, which makes treatment with radium at a distance entirely impractical. The distance in the application of radium is measured in millimeters, while most commonly the X-rays are used at a distance of 20 to 50 or even 100 centimeters. Therefore, radium is used in deep-seated malignant disease only when it can be inserted into the diseased area, as in carcinoma of the uterus, when located in some of the cavities, or when radium needles containing the radium emanation or radium element can be distributed evenly throughout the malignant tissue.

**Radium** may be regarded as most efficient for the cutaneous epitheliomas. Two forms of malignant tumors were so susceptible to it that it became the treatment of choice, *viz.*, the cellular carcinoma originating in the testicle or ovary, and the lymphosarcomas, particularly in the early stages. Almost specifically benefited also were the myelogenous leukemias with enlarged spleens. Of 425 cancer cases treated, 120 showed complete retrogression, 110 being known to be free from the disease; of these 66 were cutaneous, so that 44 represented complete retrogressions of the more malignant forms of cancer. H. H. Janeway (N. Y. Med. Jour., Sept. 8, 1917).

In a collective report of 642 cases of cancer and allied conditions treated

by **radium** at the Huntington Hospital of Harvard University, the writers conclude that many cases of advanced, inoperable or recurrent cancer may be given benefit by treatment with radium. In such cases the relief may include one or more of the following advantages: Relief of pain, diminution of discharge, less offensive discharges, relief of hemorrhage, diminution in the size of tumor masses, even to their total disappearance, and improvement in the general condition of the patient.

Among the conditions in which radium treatment has proved of special value may be mentioned: Recurrent or inoperable carcinoma of the cervix or of the body of the uterus, Hodgkin's disease and malignant lymphoma, myelogenous leukemia, inoperable squamous-cell carcinoma of the tongue, jaw and buccal mucous membranes, in non-metastasizing epidermoid cancer and in the more benign lesions of keratoses, papilloma, and other so-called pre-cancerous conditions. Duane and Greenough (Boston Med. and Surg. Jour., Dec. 6, 1917).

**Radium** reactions are painful in certain cases, which is one reason for withholding the treatment in hopelessly advanced cases. Generally, rapidly growing cellular tumors respond rapidly to radiation, but the end-results are equally unstable, because of the danger of early and widespread metastases. Neoplasms which tend to remain localized and metastasize late are most amenable, and those extending through the lymphatics are usually more amenable than those spreading through the blood stream. Nerve and dense fibrous tissues are more resistant than epithelial tissue. It is best to give 1 large dose to obtain complete regression of an epithelial tumor, for later inflammatory reactions are distinctly painful and lower the patient's vitality.

Radium may be applied as filtered radium placed on the surface or at a distance from it, and as unfiltered **radium emanation** buried in the tumor. Radium emanation decreases in value at a definite rate, and thus

can be measured. All of the radiation is utilized and normal tissues are spared useless radiation. A very marked lymphocytic infiltration is induced, and this is the greatest single defense of the body against invasion. In conjunction with surgery, emanation may be buried at any suspicious points within the wound, without interfering with healing. This method is particularly valuable in neck operations. Frequently a mass is surgically exposed and then found to be inoperable. If there is doubt, emanation tubes should be buried uniformly throughout the mass and the wound closed. Complete regression over periods of from 1 to 4 years has followed this treatment.

Little has been done with radium in carcinoma of the stomach, but rectal cancer has shown good results. One of the best fields for it is carcinoma of the uterus, particularly of the cervix, for in the best hands, carcinoma of the cervix has passed out of the operative field. Teratoid carcinoma of the testicle produces spectacular results, but these are not usually permanent. With parotid tumors results have usually been successful. Douglas Quick (Jour. Med. Soc. of N. J., Nov., 1921).

In *apparently hopeless cases* of cancer, the writer converts the deep-seated growth into a superficial one by **excising** the diseased portion as radically as is consistent with safety, and leaves the wound open, no matter how large, so that the radio-active substance can be introduced into the bottom of the cancer bed. The **radium** dosage is driven to a point where it injures the normal surrounding tissues, though not in proximity to the large blood-vessels. **Plastic operations**, when necessary, are not done until there seems reasonable certainty that the cancer will not recur, usually about a year after operation. Of 100 apparently hopeless cases treated by these procedures about 15 were saved. E. G. Beck (Internat. Clin., i, 122, Ser. 32, 1922).

**Radium** may prolong life considerably in *sarcoma*, and is superior to deep

**X-ray treatment.** In a case of inoperable *osteosarcoma of the sternum*, radium needles used after the X-ray had proven inactive led to necrosis and discharge of the tumor mass, leaving a cavity which soon healed; 20 months later there was no recurrence. In an inoperable *iliac sarcoma* treated with buried radium tubes and application of radium in the vagina and iliac region, life was prolonged for about 2 years. P. Barbarin (Paris chir., Nov.-Dec., 1923).

The more embryonal in type the tumor cells, the more effective is **radium**. All tumors of lymphatic tissue, if accessible, are amenable to it. In metastasis to lymph glands, the writer prefers buried radium element, followed by external application of radium or the X-ray. Such glands should be removed only after thorough radiation. Cancer in proximity to large vessels and nerves should be treated with radium. In mammary cancer buried radium greatly aids the effects of the X-ray. It is also indicated in cancer of the prostate and bladder after surgical exposure, in recurrent glioma of the orbit, cancer of the tonsil, and in general, to conserve tissue if needful, as in certain advanced lip cancers or where the entire cheek is infiltrated. W. H. Schmidt (Amer. Jour. of Roentg., Sept., 1924).

Late results of radiation in cancer dealt with in a study of cases treated since 1910 in a cancer hospital. Nearly all were treated with **radium**, some receiving **X-ray** in addition. In superficial, freely movable *skin cancer*, cure was obtained in 86.3 per cent. of 102 cases, while in infiltrating, fixed skin cancer, 51.4 per cent. of 105 cases were cured. This series included entirely inoperable cases and cases in which treatment was uncompleted. Of 40 cases of superficial *cancer of the lower lip*, 90 per cent. remained well after 5 years, and of 26 infiltrating cancers, only 34 per cent. In less than 10 per cent. of 257 cases of cancer of the skin or lip primarily recovering under radium did recurrences later occur which could not be cured by repetition

of radium treatment. Of 505 cases of *cancer of the cervix*, 40.5 per cent. of the operable or borderline cases were free of symptoms 5 years after radium treatment, and 16.6 per cent. of the inoperable cases. G. Forssell (Amer. Jour. of Roentgenol., Oct., 1924).

Summary of results of **radium** treatment of *cancer of the uterine cervix* in Döderlein's clinic. In all cases 5 years of observation had elapsed. Of 755 cases treated from 1912 to 1918, 110 were operable cases, with 43.6 per cent. of cures; 130 were borderline cases, with 22 per cent. of cures; 340 were inoperable cases, with 6.7 per cent. of cures, and 169 were hopeless cases, with 1 cure. The figures for 1918 and 1919, covering 272 patients, were essentially the same. Voltz (Klin. Woch., July 16, 1925).

D. Turner (Brit. Med. Jour., Mar. 17, 1923) states that the following forms of malignant disease admit of cure by **radium**: Rodent ulcer; epithelioma; lymphosarcoma; spindle cell sarcoma; sarcoma. The following admit of relief by radium: Carcinoma; lymphadenoma; spleno-medullary anemia.

The use of the other radioactive substances, such as **actinium** and **mesothorium**, in the treatment of cancer has been attended by an indifferent degree of success.

**Finsen Light.**—Early in the use of this remedy it was thought that it would be able to reach deep-seated neoplasms, so marvellous were the results obtained by its use in lupus. But experience has shown that its powers are very limited, and, although with very careful manipulation superficial epithelioma may be overcome by it, it is powerless to favorably affect lesions which are at all deeply seated.

A few days after **electrocoagulation** of squamous-cell epitheliomas, the writer uses the **Finsen water-cooled rays**, which he regards as assisting

greatly in the resulting cosmetic effect. The rays are asserted to stimulate granulation as well as to aid in the elimination of by-products that are harmful to the growth of new cells. R. C. Lounsberry (Jour. Mo. State Med. Assoc., Jan., 1925).

**Leucodescent Lamp.**—Much the same may be said in regard to the leucodescent lamp, which has been tried and found wanting.

It is questionable if the leucodescent lamp has any value as a curative agent, but the heat given off will often be of value in alleviating the pain of ulcerating lesions.

**Fulguration and the Electrothermic Methods.**—These additions to the non-surgical treatment of cancer appear to have promise, although some have been skeptical as to the real value which has been claimed for them.

**Fulguration** is in reality only the employment in an exaggerated degree of what has for some time been found of value in certain other conditions, namely, a strong high-frequency current, in a manner proposed by Keating Hart, of Marseilles. As developed by Czerny, the patient, under an anesthetic, receives intense brush discharges from a metal electrode at a distance of from  $\frac{3}{4}$  to  $1\frac{1}{2}$  (by some; 5 to 6 in. by Dr. Keating Hart) inches, and for from 5 to 40 minutes. After this the cancerous part is removed by the knife or a sharp spoon, and the wound is exposed again to fulguration, to kill any remaining cancerous cells. A destruction of tissue is effected for hardly  $\frac{1}{2}$  inch beneath the surface, so that in large growths a preliminary removal by the knife or curette is recommended. Keating Hart maintains that the high-frequency spark possesses a special predilection for the cancer-cell, even to the

extent of reaching metastases in regionally enlarged lymph-nodes.

Keating Hart reported a healing of 95 per cent. of cancers of the skin, 40 to 50 per cent. of cancers of the breast, and 20 to 25 per cent. of cancers of the mucous membrane. Czerny concluded that fulguration will cure superficial, soft, cancerous ulcerations, and stimulate healthy granulation to a marked degree. In indurated and more deeply infiltrated carcinoma a previous excision of the growth must be performed. In deep-seated cancer fulguration finds a very limited sphere of utility. In inoperable and recurrent cancer fulguration can successfully affect the itching, bleeding, and pain.

Other observers have more or less confirmed the claims which have been made for fulguration.

The presence of *pigment* in a cancer should be a warning to refrain from radiotherapy. Nothing but **electrolysis** can arrest the progress of these tumors, and this only when applied early. Another contraindication is deep involvement of the wall of the esophagus or other organ, radiotherapy only hastening the end by inducing perforation. Laborde (Ann. de méd. de Paris, Mar., 1922).

W. L. Clark, J. D. Morgan and E. J. Asnis (Radiol., Apr., 1924) consider **electrothermic methods** of cancer treatment as second to none, though surgery, radium and X-rays are all indispensable likewise, alone or in combination, to meet particular indications. Their procedure is entirely dissimilar from and superior to Keating Hart's fulguration, the thermocautery, galvanocautery and electrolysis.

In the **desiccation** method, as described by these observers, heat is applied which is just sufficient to desiccate or dehydrate the tissues. The heat is produced by a monopolar high-frequency current of the Oudin

type, and applied with a steel needle or other pointed applicator. Desiccation is used advantageously when the lesion is localized and good cosmetic results are essential. It results in little trauma to the tissues, little secondary inflammation and little scarring, and is therefore useful in removing growths from delicate structures such as the cornea and vocal cords. It is an important measure in malignant lesions of the skin and mucous membranes, as well as in many non-malignant conditions. **Coagulation** is a procedure distinct from desiccation and is produced by a bipolar high frequency current of the d'Arsonval type, using a multiple spark gap. It is more penetrating and intense than desiccation and is used for larger growths, even those involving bone. An indifferent electrode is required, and a current strength of 200 to 2500 ma. is used. Unlike the actual cautery, the heat is generated within the tissues by their resistance to the current, and a deeper action results.

With either desiccation or coagulation, the aim is to destroy the growth at a *single operation*. The devitalized tissue is, as a rule, immediately removed either by **excision** or **curettage**, usually accomplished without hemorrhage; on mucous surfaces, however, the destroyed tissue is usually allowed slowly to separate. The vitality of the surrounding normal structures is conserved by these methods. The latter should be used alone only in localized tumors of a type which does not tend to metastasize. Basal cell epithelioma of the face, eyelids, etc., even though extensive, and with bone involvement, may be so thoroughly treated that recurrences are infrequent. In localized squamous-cell epithelioma of the skin or mucous membranes, the results are almost as good; if metastasis has already occurred, other methods must be used in addition. In the bladder, larynx, etc., endoscopes are used to render the growth accessible to treatment. Malignant cells, especially the least differentiated, are devitalized at a lower degree of heat than normal cells. Histologically, desiccation results in a shrunken, elongated, mummified appearance of the cells and their nuclei, with round cell infiltration, while coagulation produces complete loss of cell outlines, a hyalinized appearance of the tissue, and thrombosis of the vessels. Good results are reported in advanced cases of cancer or sar-

coma of the nasal region, orbit, ear, eye, tongue, etc.

In superficial malignancies, the writer proceeds as follows: All the growth projecting above the normal skin is destroyed by **electric coagulation**, after injecting **novocaine** with a little **adrenalin**. The burned tissue is carefully **curetted** away and the base of the ulcer thoroughly heated with the **electric current**. The unfiltered **X-ray** is then used to destroy any cells lying deeper in the tissues. Any of the cancer tissue which is covered by normal epithelium is exposed by the electric coagulation. The main object is to expose all the cancer tissue and form an open ulcer. If there is much thickening and induration around the base of the ulcer, **radium needles** are imbedded and left for 5 to 8 hours. Some cases receive all 3 treatments—X-ray, coagulation, and radium. The patients are given instructions about keeping the ulcer clean and asked to return in 1 month for observation, the large majority being then healed. C. F. Bowen (Ohio State Med. Jour., Jan., 1922).

The **electrothermic method** is very effective in basal-cell epithelioma of the face and extremities, cancer of the lower lip, cancers in the mouth, and for the destruction of indolent sloughs resulting from radium. It absolutely destroys all disease without devitalizing normal tissue, and healing is rapid, with a soft, pliable scar. Only rarely can the results not be improved by the use of 2 or more methods in a given case. W. H. Schmidt (Amer. Jour. of Roentg., Sept., 1924).

**Monopolar endothermy** (desiccation) advocated. In accessible epidermoid carcinoma, using as electrode an ordinary sewing needle in a suitable handle, the writer first makes a light ring of destruction in healthy tissue around the malignant growth. A specimen for the microscope is then taken with impunity, after which the growth itself is attacked with the needle and destroyed *in situ*. It is then curetted away, the clean base seared over with a brushing of the current, and a dress-

ing applied. G. A. Wyeth (Boston Med. and Surg. Jour., Oct. 9, 1924).

The **endothermy knife** is a recent development of a current of much higher frequency, dependent upon the more modern tube system for its oscillations. The current produces the effect of cutting without the use of a sharp knife. By searing as it cuts, it leaves a sterile incision. It supplements, but is not a substitute for, either monopolar or bipolar diathermy. G. A. Wyeth (N. Y. State Jour. of Med., Oct., 1924).

Mr. Woolpert, a Harvard Cancer Commission research worker, has found that **ultra-violet light** alters protein so that it coagulates at a lower temperature than unexposed protein. The use of ultra-violet light followed by the application of **diathermy**, with immediate exposure to **X-ray**, will probably give a maximum of result to the X-ray.

Tissue dominance, which is closely related to cancer growth, is closely associated with metabolic activity. This has been shown by Child, Hyman and others. It is at the period of greatest metabolic activity that the cells are most influenced by radiations, whether the ultra-violet rays, X-rays or radium. Bovie, in his report to the Cancer Commission of Harvard University in 1923, stated that phenomena that have been observed lead to the belief that the organization of protoplasm has its origin in the orientation (or polarization) of the molecules at the inter-foci of the protoplasmic constituents, and that this organization is broken down under this (ultra-violet) radiation. Cancer seems to be more prevalent in regions where cloudy atmosphere prevails than in those areas where sunlight is more constant. Benoit found Southern France,

where sunlight is greatest, to have less cancer than Northern France, where cloudy weather is more frequent.

Changes in the cell such as pyknosis in the nuclei and the formation of monstrous cells may be produced by heat, by diathermy, by freezing or by certain chemicals. These are practically the same changes as are produced by diathermy. For this reason it has been assumed that the action of X-ray would be enhanced by prior treatment with heat in the form of diathermy.

In *basal-cell* epithelioma of the *face*, which rarely metastasizes, complete destruction of the growth from the beginning is aimed at. This is done by **electrocoagulation** with the high frequency spark, followed with a full erythema dose of the **X-rays**. In *squamous-cell* epithelioma, which gives rise early to metastasis, the lesion is destroyed by electrocoagulation, followed by either X-rays or **radium** used locally and upon the adjacent glandular areas to the point of saturation of the tissues. Epithelioma of the *tongue* can be treated successfully by similar means. Pfahler and Widmann (Jour. Maine Med. Assoc., Apr., 1922).

Combined treatment by **surgical diathermy** and the **X-ray** offers better promise of a permanent cure than either method alone. Whenever possible, the author irradiates the affected area both before and after the coagulation treatment, as well as later, after healing has occurred. The high-voltage X-ray treatment is employed. A. L. Yocom, Jr. (Jour. of Radiol., July, 1924).

**Sera and Vaccines.**—The treatment of cancer by **sera** is based upon the assumption that immunity of some kind can be created against cancer. There are many facts which warrant such a view, with considerable evidence which is to be found in experimental cancer among animals.

An active immunity exists against



the successful inoculation of cancer of one animal into another of a different species, and a certain degree of active immunity against the successful inoculation of cancer from one animal into another of the same species, but of slightly different variety. V. Leyden found that the tumor which Jensen discovered in mice and first described could be transplanted with ease (in 70 to 80 per cent. of the cases) into mice of Copenhagen, but could not be transplanted to Berlin mice.

Borrel could only transplant the same tumor in 30 to 40 per cent. of instances into the Parisian mice. Haaland obtained a series of sarcoma takes in 97 per cent. of Berlin mice and only 24 per cent. of takes in Hamburg mice. A tumor composed of mixed sarcoma and carcinoma gave in Berlin mice a pure sarcoma and in Danish mice a pure carcinoma.

It has been found that in both mice and dogs—indeed, in all animals—a very strong degree of active immunity exists against inoculation in those animals in which the tumors have spontaneously retrogressed.

An active immunity against the successful **inoculation** of a tumor may be induced in an animal by the injection into the animal of certain normal tissues, liver (Borrel), and blood of other mice or rats (Woglom); by the injection of **splenic tissues**, of **embryonic tissues**, and finally by the **tumor tissue**, killed by fragmentation or reduced in virulence by heat. The degree of active immunity thus resulting is greatest if the tissues used for the injection are closely related to the tissues from which the tumor originated; thus, it is the skin of mice embryos which is most effectual

against certain epitheliomas in the mice, and hashed flayed embryos will produce no immunity against inoculation (Bashford, Murray, and Haaland).

It must be remembered, however, that animals which have been rendered in this way immune to the inoculation of tumors may later develop spontaneous tumors of their own; so that this form of immunity is a very different thing from active immunity against the growth of tumor tissue in general.

It is generally difficult to reinoculate an animal in which a tumor is already growing, but our ability to produce in this manner an artificial metastasis depends to some extent upon how rapidly the inoculated tumor grows. If the tumor is a very rapidly growing one, a second inoculation will frequently not succeed, and also frequently, if the tumor is growing poorly and certainly if it is retrogressing, a reinoculation never succeeds. **Reinoculation** frequently succeeds in tumors with a moderate or normal rate of growth. After complete extirpation of a tumor Schöne found in mouse carcinoma that reinoculation succeeds; on the other hand, in tumor with a moderate rapidity of growth after incomplete excisions reinoculation may be unsuccessful. These results have been confirmed in rat sarcoma by Uhlenhuth, Handel, and Steffenhagen.

A passive immunity may be induced by the **serum** of healed animals. When such serum is mixed with the cancer cells inoculation with these cells will produce a very much diminished number of takes.

Further than this, Clowes and Baeslack (Jour. of Exp. Med., viii.

481, 1906) cured 12.3 per cent. of mice with tumors by injecting such a serum. Borrel has treated successfully a mouse tumor with the serum of a sheep which had been previously injected with mouse-tumor tissue.

Beebe has shown that it is possible to cure dogs with lymphosarcoma by bleeding them and transfusing them with the blood of animals in which a spontaneous retrogression of the tumor has taken place. The blood of a normal animal, though exhibiting some tendency to cure other dogs, was in no case so successful as the blood of immune animals. The blood of immune animals, however, is not alone sufficient. It must in some way initiate a reaction in the tumor. There is also evidence to show that growing tumors are necessary at the time of transfusion in order to cause the retrogression of the tumor. If, for instance, the transfusion is performed five days before the implantation, a retrogression of the tumor implanted will not occur.

Von Dungern and Sticker state that there can no longer be any doubt about the existence of immunity against transplanted tumors in mice, and, we may further add, of tissue specificity in the matter of this immunity.

Bashford (Fourth Report of the Imperial Cancer Research Fund) sums up his conclusions from the facts and his own work in the following words: "Resistance to inoculation is induced only by living cells, either cancerous cells or normal cells of the same species. Under similar conditions the cancerous cells and the normal cells of strange species are both devoid of the power to induce resistance. An animal's own tumor

and its own normal tissue are devoid of this power, and the means which prevent the successful inoculation of the tumor of another individual do not prevent the successful inoculation of an animal's own tumor. Tumor tissue usually induces resistance against itself quite as well as and, with regard to the phenomenon of spontaneous healing, much more effectively than, any other tumor. Furthermore, animals which have proved resistance to repeated inoculations of a tumor have subsequently developed spontaneous tumors showing progressive growth. These experimental inquiries into the production of growths by inoculation on the one hand and its prevention on the other hand agree in demonstrating individual relations as obtaining between a tumor and the animal in which it arises."

The question next arises, What is the nature and mechanism of this immunity? Ehrlich attempted to explain the immunity of cancer by a hypothesis to which he gave the name "atrepsia." He assumed that certain specific food substances are necessary for the growth of the cancer cell; that these specific foodstuffs are present in limited amounts, and that whether they are available or not for the cancer cells depends upon the relative avidity of the receptors of the cancer cells and the normal body cells for these specific foodstuffs.

The tendency at the present time, however, is to accord to cancer a true antibody immunity.

As Von Dungern showed, the persistence of immunity after the retrogression of tumor tissue could not be explained by the absence of specific foodstuffs. Certain reactions of an

anaphylactic character are originated by the introduction of tumor cells into immune animals. These are edema and, in particular, a collection of plasma cells, lymph cells, and monophages in large numbers.

*Passive immunization.*

I. Normal serum therapy (sera of healthy animals).

II. Serum therapy by immune sera.

Cellular serum therapy; antigen from neoplastic cells and their derivatives.

Natural cellular serum therapy; serum from healed or cancerous animals.

Artificial cellular serum therapy (cytolytic serum).

Parasitic serotherapy.

Bacterial serum therapy.

*Active immunization.*

Cellular vaccines; the cells of new growths modified or intact.

Non-bacterial serum therapy, yeasts.

Autocellular, heterocellular, and xenocellular vaccines.

Parasitic vaccine therapy.

Bacterial vaccine.

Non-bacterial yeast; coccidia.

Bacterial toxin therapy.

Toxin of bacterial origin; xenobacterial toxin.

Non-bacterial toxins.

All other parasites, yeasts, and molds.

active and passive immunity in human cancer.

Vidal has given the following classification of the various methods by which it has been attempted to produce immunity in human cancer:—

Autocellular serum (patient's serum; antigen from tumor or from same patient); healed cellular serum (serum of healed animals).

Cytolytic xenocellular serum (cytolytic serum; etiological cellular serum; antigen from histologically allied cells, epithelioma, sarcoma).

Bacterial serum (etiological) derived from (antigen) pretended cancer bacteria; antigen derived from bacteria not etiologically related to cancer.

All parasites from indifferent (etiological) sources.

Tumor of same patient; tumor of another species of animal; material foreign to the neoplasm.

Any bacterial vaccine (bacteria maintained to be the cause of cancer); xenobacterial vaccine (non-cancerous bacteria; streptococcus).

All foreign bacteria.

Toxin of cancer bacteria; toxin of non-cancerous bacteria.

De Fano also noticed cellular reactions in immune mice, though they have been missed in non-immune animals. Von Dungern attributes these to the action of an antigen.

Turning from the realm of experimental cancer to human cancer, one will find most of the facts in the former duplicated by the latter. There unquestionably exists both

All of these methods of producing immunity in a patient suffering with cancer for the purpose of curing the disease have been tried with a greater or less degree of claimed success.

Representing the auto- and heterocellular vaccines, numerous attempts have been made to produce immunity by the injection of comminuted or ground-up cells of the patient's own

tumor or of another tumor of similar histological structure or of extracts of these tumors. In some instances, remarkable success has attended such trials. The most noted paper upon this subject was by Coca and Gilman (Philippine Jour. of Science, B, iv, 391, 1909).

Janeway witnessed a large sarcoma of the neck apparently healed by the injections of autogenous vaccines.

The results of Coca and Gilman cannot be neglected even though the subsequent work of the same writers did not confirm their first results. They prepared a suspension of the finely divided tumor in normal salt solution and alcohol, to which a small quantity of carbolic acid was added as a preservative. The patients were injected with this material. None of them showed any ill consequences. Three of the patients who possessed inoperable growths showed marked improvement, the growth softening and disappearing. Fourteen of the patients were subjected to operations, most, but not all, of the tumor being removed. After seven or eight months no recurrence took place. All the tumors treated were of the epithelial or glandular variety.

Although Coca and Gilman's results have not been repeated by others, they are yet important because they indicate some impression on carcinoma by agents of this class.

Small, Evans and Krumbhaar (Jour. of Cancer Res., Sept., 1925), in describing studies upon tumors and their relationship to increased biological resistance in animals which have received injections of irradiated tumor tissue, state that they were much gratified with the injection of cancer extract and had thought that some of their cases were

doing exceedingly well, only to meet with failure in the very next patient. It is possible that there is a biological variation in the protoplasm of the tissues of the patient himself that produces variation in the results. The whole question is ill-defined.

Lumsden (Lancet, Feb. 21, 1925) found that by injecting immediately after operation tumor cells of analogous type but not those of the tumor present in the patient, a resistance to the growth of the type with which the animal was affected occurred.

Dungern's demonstration of the feasibility of producing an epithelial immune serum referred to, and likewise Ehrlich's experimental immunity of mice to carcinoma by inoculations with avirulent tumor cells. The author's own procedure consisted in the preparation of a **tumor emulsion** by grinding 1 Gm. of tumor with 8 c.c. of normal saline solution; 20 per cent. and 50 per cent. dilutions of the emulsion were then made and the cells killed with 0.5 per cent. phenol. Clinically he injected subcutaneously increasing doses of emulsion every six days, ascending from 0.2 c.c. of the weaker emulsion to 3 c.c. of the stronger. The entire treatment lasted four or five months. The aim was, after radical operation and with absence of metastases, to prevent recurrence. Out of 14 cases dealt with, 10 remained free of recurrences and out of the 4 recurrences, only 2 were fatal. He believes these injections of homologous material more effective than postoperative X-ray treatment. F. Keysser (Arch. f. klin. Chir., Oct. 17, 1921).

An **autolytic product** was found effective in several cases of basal cell cancer. It was prepared by subjecting cancer tissue to autolysis for 1 to 3 days in the incubator, sterility being insured thereafter by heating at 56° C. on several successive days. Marked improvement or even "temporary cure" followed the treatment. Lamprecht (Derm. Zeit., Apr., 1924).

Hodenpyl (Med. Record, lxxvii, 359, 1910) made the attempt, possibly based upon another principle, to cure carcinoma by the injections of **ascitic fluids** from cases of carcinoma, but particularly from cases in which the cancer had shown retrogression.

Concerning the use of **xenocellular vaccines**, attempts have been made by Braunstein (Berlin. klin. Woch., xlviii, 2029, 1911) to treat cancer with the injection of **splenic pulp**. Experiments on animals affected with sarcoma were very successful.

R. Oestreich (Zeitschr. f. Krebsforsch., xi, 44, 1911), noticing that cartilage and the tissues of the arterial walls are rarely attacked with cancer, and that these tissues are rich in **chondroitin sulphate of sodium**, has attempted to cure cancer by injecting the latter substance under the name of antitumin. He used the remedy subcutaneously. Sections from the treated cases, all late cases of cancer, showed considerable necrosis and leucocytic infiltration and a marked clinical reaction.

In line with the suggestion furnished by animal experimentation, and also in view of the rarity of cancer in the young, Fichera (Policlinico, xvii; Sez. prat., 845, 1910) treated cancer by the injection of **autolysates of human fetuses**. The hashed tissues are mixed with 20 parts of physiological salt solution, to which a little thymol or phenol is added. This mixture is covered on top with toluol and kept at 37° for two months. The suspension is then tested for its sterility and injected in quantities of 2 to 3 c.c. two to four times a week.

He treated in this manner 36 cases of inoperable cancer. Only 18 of these were given a thorough course.

Eight of the patients did not seem to be benefited, but in 10 others a favorable influence was unmistakable. In 5 patients the malignant growths entirely disappeared. Of these 5, the cancer was in the breast in 3, in the thyroid in 1, and in the rectum in the other.

Although, for the present at least, **parasitic vaccine therapy** and **bacterial toxin therapy** are not entitled to serious consideration, with the exception of Coley's attempts with the mixed toxins of the streptococcus and *Bacillus prodigiosus*, yet brief mention may be made of Otto Schmidt's **cancroidin** or **antimeristem**. Schmidt (Zentralbl. f. Bakt., 52, 11, 1909) considered that he had discovered in his mucorracemus the cause of cancer. Injections of pure cultures of his organism had caused, he believed, malignant tumors in animals, and the injection of killed cultures had cured sarcomatous rats. He reported several cures without recurrences in women suffering from uterine cancer. A few cures were reported by different authors. Others, however, had no success with the method.

One of the most interesting methods of treatment is that which resulted from observing the disappearance of sarcoma after an intercurrent attack of erysipelas. This led to the treatment of certain forms of sarcoma by the **mixed toxins of the streptococcus of erysipelas** and *Bacillus prodigiosus*, with which the name of Coley is inseparably connected, and which certainly demands attention, although the success following its use by others does not equal that reported by him. In a classical article he reported the treatment of 71 cases by this method; of these, 40 were in patients treated three or more years

previously. Of these 40 cases, 10 were not traced, but of the 30 remaining (including one case in which the diagnosis was doubtful), 10 have been regarded as permanently cured; another case remained well for five years, and then died of general metastases. Two of the cases had inoperable sarcoma of the femur, one of which was periosteal; in another case there was an incomplete operation on the head of the femur; the mixed toxins were then used, and a permanent cure of nine years resulted.

Coley stated that he had had 40 per cent. of successes in 37 cases of inoperable sarcoma. The tumors disappeared under the use of the injections of the mixed toxins of erysipelas and *Bacillus prodigiosus*.

The 2 dangers which deserve consideration are the danger of death from collapse from too large an initial dose and the danger of nephritis from long continued treatment with very large doses. Out of nearly 1000 cases only 3 deaths occurred during treatment and in 3 other cases nephritis developed, so the danger might be said to be negligible.

There are 5 indications for the use of the toxins: 1, in practically all cases of inoperable sarcoma; 2, before operation in sarcoma of the long bones; 3, immediately following incomplete operations in which part of the tumor could not be removed; 4, in combination with radium or X-rays, and, 5, after all operations for sarcoma and carcinoma in the hope of preventing recurrence. In addition possibly also toxins should be used in certain cases of inoperable carcinoma, though this is experimental; nevertheless, a few good results have been obtained. In the series of 1000 cases, the disease apparently disappeared in 97; 74 remained well and free from recurrence from 1 to 24 years; 66 from 3 to 24 years, and 13 from 15 to 24 years. The greatest success was obtained with the toxins in sarcoma of the long bones

and lymphosarcoma. W. B. Coley (Trans. N. Y. Acad. of Med.; N. Y. Med. Jour., Sept. 8, 1917).

[See also COLEY'S FLUID, Vol. III.]

Turning now to the attempts to heal cancer by the use of methods transferring **passive immunity**, one will find that the field is not altogether barren of results.

Very little of value has been accomplished by the use of **normal sera**. Aside perhaps from a few rodent ulcers of the skin no actual cure has been accomplished. Some cases of cancer have been temporarily benefited, judging from the clinical symptoms.

Stress laid on the protective properties of the **blood of young individuals** against cancer. **Injections of serum** from the patient's children or grandchildren, sometimes in conjunction with stimulating radiation, proved to have a marked effect on the blood as well as on the tumor itself. In one case an extensive carcinoma of the temple healed with a good scar, and in another, a hard gastric growth of the size of a fist disappeared. J. Wetterer (Deut. med. Woch., Apr. 14, 1922).

Hodenpyl's efforts, which attracted considerable attention in this country, should be classed in this category. He obtained an **ascitic fluid from a patient with a retrogressing cancer**; a most favorable effect was noticed upon human beings with cancer injected with this fluid. He treated altogether 47 patients, almost all of whom were distinctly unfavorable ones; considerable improvement was obtained in many of them. Due to Hodenpyl's unfortunate death, his preliminary report was the only one published, and the promised details were, therefore, never given to the profession. His work is exceedingly

difficult to repeat on account of the difficulty of securing patients with retrogressing tumors. Injection of a simple ascitic fluid in patients with advancing cancer has given practically no beneficial results.

Attempts with serum from patients with advancing growths have been barren of results. Hodenpyl's work should, however, be borne in mind, as cases with retrogressing malignant new growths are met with from time to time. Mackay (Brit. Med. Jour., ii, 138, 1907) collected 50 authentic cases of a more or less complete spontaneous retrogression of cancer growths.

Risley (Boston Med. and Surg. Jour., clxv, 127, 1911) reported 10 cancerous patients treated with fluids from non-cancerous patients and 45 cancerous subjects treated with serum from other cancerous cases. No favorable change was noted in any of the 10 patients treated with sera from non-cancerous subjects. In practically all of the 45 patients treated with the serum from cancerous subjects, there was some local or general reaction. An apparent retardation of the growth occurred in 8 cases for a period of two to five months; 12 patients remained in excellent condition, gaining strength and weight during the treatment. In no case was there an actual shrinkage in the tumor.

**Autoserotherapy** was used by Gaudier (Bull. de l'Acad. de méd., July 12, 1921) in 24 cases, involving the tongue in 8 instances; the pharynx in 6; nasal cavities and sinuses, 4; breast, 3, and scalp, 1, together with 2 cases of intracranial sarcoma. Twenty c.c. (5 drams) of the patient's blood was collected and the serum from it injected subcutaneously the next day. The average amount of serum was 10 c.c., and 20 such in-

jections were given at 3-day intervals. Subjective relief sometimes set in after the initial injection, and later there occurred gradually a reduction in the size of the tumor, and of ulceration and glandular enlargement, and an improvement in the general condition. Cachectic and debilitated patients were enabled to resume their former activities and mode of life.

**Autoserotherapy** advocated as a procedure serviceable for the relief of pain and insomnia, restoration of appetite, and general reactivation in cancer cases. The writer obtains 20 or 30 c.c. of the blood from a vein, places it in the ice-box for 24 hours, warms the serum from it to body temperature, and injects 10 or 15 c.c. of it intravenously. Only exceptionally does a temperature reaction follow. Three injections at weekly intervals are usually given. Aside from the constitutional improvement, there results also more or less reduction of the local discharge and of the size of the tumor. Endler (Arch. f. klin. Chir., cxxvi, 176, 1923).

Passing to the consideration of the artificial cellular serum therapy and the various **cytolytic sera**, a number of apparently definite results are on record.

Nee in 1895 first laid the foundations of humoral reactions and of the creation of cytolytic antibodies. At a later day von Dungern took up the work and first showed the very great specificity of cytolsins. The intensity of this characteristic almost led to an abandonment of these methods.

Then, Richet and Héricourt took up the work with cytolsins obtained by injections of dogs and donkeys with macerated tumor tissue, together with their immediate followers. In 1906 there had been 120 experiments of this kind upon human cancer. The results were a varying degree

of softening and reduction in size of the growth, a diminution of pain and edema, and a definite cicatrization. In some cases hemorrhages ceased and discharge lessened, and in most cases marked improvement in the general condition resulted.

Vidal continued investigation in a seemingly systematic manner. He found, applying the Bordet-Gengou method, that two substances are concerned in the action of a specific cytolytic serum developed in a dog by injecting the same with human epithelioma, one comparable to the amboceptor, thermostabile, and the other comparable to the complement and thermolabile.

The following classification represents, according to Vidal, the various physicochemical conditions in which the antigen may be obtained:—

- A. Chemically normal cells. I. Absolutely fresh emulsions.
  - 1. By glycerin.
  - 2. Emulsions preserved by some antiseptic, as chloroform.
  - 3. In a secondary state.
- B. Tissues physically somewhat disintegrated, as by freezing.
  - Normal albumins:—
    - (a) Soluble in water.
    - (b) Nucleoproteids.
- C. Antigens reinforced (or not) by a fraction of cellular albumins.
  - Albumins chemically modified:—
    - (c) Peptones.
    - (d) Nucleins.

Vidal found that, for greatest efficacy, the following conditions should be observed in the preparation of the antiserum: 1. The employment as antigen of a very fresh emulsion of malignant cells, sensitized by administration in an exactly corresponding antiserum. 2. Injection of a rabbit-dog serum toxic to white cells at least 6 hours preceding the injection of the

antigen. 3. Reduction of the number of antigen injections to three. 4. The blood of the animal used for the production of the antibody to be drawn at the height of leucocytosis induced by the injection of serum toxic to white cells.

One other factor of very great importance concerns the gradual development in the blood of the treated patients of an anticomplementary substance, which accounts probably for the loss in power of specific cytolytic serums, so often observed in the serum therapy of cancer.

Vidal found that action of this anticomplementary substance can be set aside both *in vitro* and *in vivo* by the use of an antiserum prepared from effusions of such refractory patients. The rarity, however, of such effusions makes such a method of treatment difficult. When once obtained, however, such sera neutralize the anticomplementary substance and are of very great value for the reason that they are not specific for any special type of cancer.

Vidal treated 94 cases of cancer in the development of these principles. Of these 94 cases, 3 received no other treatment, and were as follows: 1. An epithelioma of the tongue, verified by a microscopic examination, and of considerable size. Received 46 injections in seven months' time and 10 injections during two years following. Patient healed and living after 7 years. 2. A cylindrical epithelioma of the rectum; operation refused, and diagnosis verified by the microscope; 25 injections in one year and 13 during the next year. Well thirteen years later. 3. Epithelioma of the breast, ulcerated and inoperable; confirmed by microscopic examination.



Patient received 70 injections; was well 10 years later.

There were 48 patients operated upon and also treated with serum; 28 of these cases survived 7 years,—a higher proportion than would likely have followed operative methods alone.

In the series was a case of cancer of the cervix which refused intervention; the growth disappeared after 60 injections and the patient was well 6 years later. Another case was one of sarcoma of the trapezius which had recurred. It disappeared under serum therapy, and the patient was well 5 years later. A third case was one of very advanced tumor of the breast. The patient received 45 injections, after which a partial absorption took place, permitting a local removal of the mass. Further continuation of the serum therapy resulted in recovery, the patient remaining well for 3 years.

Among the remaining cases were 19 showing considerable improvement, equivalent in some cases to temporary cure (2 years).

These results have been confirmed to a certain degree by Beebe (*Med. Rec.*, lxxxii, ii, 1912), who developed a cytolytic serum by injecting an animal with the cancer cells and then injecting the patient with increasing doses either intramuscularly or, better, intravenously.

Little need be said of the parasitic serum therapy. Tuffier, Le Toux and Emerich and his school, and Whaef and San Felici have published some results which are far from being of the same order as those just described, comparing in efficiency rather with those obtained by the use of normal blood-serum.

Carter Wood (*Jour. Amer. Med. Assoc.*, Oct. 3, 1925), in a review of immunity in cancer, states that "it has

never been possible to demonstrate in the body either of human beings or of animals any reaction that can be regarded as a response to an immunizing quality of the tumor cells of a primary growth of whatever nature."

A sex gland serum, **tumorcidin**, prepared by the writers is claimed by them to be effective in a certain proportion of cases. Experiments had shown that such serum inhibits the growth of malignant tumors. It is prepared by injection of sex glands into normal animals, the production of substances which regulate the growth of the body cells being thus stimulated. The dose is 3 teaspoonfuls of serum by the mouth daily. Cases of improvement or clinical cure are reported, and the serum is deemed useful to prevent recurrences after operation. R. Deutschmann and W. Kotzenberg (*Deut. med. Woch.*, Apr. 25, 1924).

Cancer, then, represents various forms of misbehavior of the normal tissue-cells of the body, is apparently not caused by a parasite, and as yet has not any one means of cure. Until we know more of the ultimate causes which lead certain cells to take on what we call malignancy, we cannot formulate any intelligent plan of medical treatment. Nor are there any remedies with much specific action on cancer. The various local measures mentioned all have their limitations.

Thus far surgery offers the best percentage of results along certain lines, and modern surgery has vastly improved this percentage over that of fifty years ago. But even surgery has its limits when the disease has progressed beyond a certain stage, and not infrequently it seems unable to check the ravages of cancer at any stage.

The lesson to be learned, however,

is, just when the knife must be resorted to. The surgeons say, very properly, the earlier, the better, and plead for the immediate removal of even suspicious tumors; unquestionably far more harm results from delaying too long before resorting to operation than from operating too early. The judgment of the physician, therefore, should ever be free and unbiased, and the claims put forth in favor of this or that method of treatment should not cloud the judgment of the physician or patient as to the proper claims of surgery, nor should operative interference be delayed so that the chances of cure offered by surgical procedure are lessened.

A recent essential change in our views of cancer is an acceptance of the modern idea that the duty of the physician to his patients is now to recognize, diagnose, and treat radically the conditions which ordinarily precede cancer. The general principle is immediate removal of any mechanical or physiological irritation which could conceivably cause an existing thickening or ulceration, and if this is not followed by prompt disappearance of the lesion, an immediate and thorough excision of the induration or ulcer while still benign. The following are pre-cancerous conditions which are not malignant: Moles (especially pigmented), keratoses, ulcers of skin and orifices, gall-stones, ulcers of stomach, ulcers of mouth, cystitis, erosions of cervix, premature or obstructed involution of breast, uterus, or prostate, the adenomata, the papillomata. Cysts in the ovary and breast (because they tend to develop papillomata of their linings), polyps of uterus or rectum, and, in general, all epithelial neoplasms.

In squamous epitheliomata of the surface and carcinomata originating in the follicles of the skin, radiation, cauterizing agents or freezing mixtures may be employed in the early stages; if any suspicion of malignancy

arises, however, they should be radically removed, together with the nearest set of lymphatic glands. Any chronic lump in the breast which has persisted for a month without decrease should be removed. E. Reynolds (Boston Med. and Surg. Jour., Aug. 1, 1918).

Regarding the relief of pain, patients who cannot take morphine alone will tolerate it in combination with scopolamine. With doses of 0.0006 Gm. ( $\frac{1}{100}$  grain) of scopolamine and 0.03 Gm. ( $\frac{1}{2}$  grain) of morphine the "atropine symptoms" predominate over the morphine symptoms. Scopolamine is suitable for prolonged treatment of painful organic diseases. As habituation develops for atropine, as well as for morphine, the daily dose must be gradually increased. The use of scopolamine for 2 years in a case of cancer cachexia kept the patient comfortable and prolonged her life. Lewenstern (Polska gaz. lek., Jan. 29, 1922).

To subdue pain in cancer cases, the writer regularly uses quinine, injecting 20 or 30 c.c. (5 to 8 drams) of a 10 per cent. solution on alternate days and giving 2 tablets, each containing 0.5 Gm. ( $7\frac{1}{2}$  grains), by mouth on the intervening days. This plan is followed for 20 days, the series being later repeated if the pain recurs. The drug also exerts a tonic action. J. R. Goyena (Sem. méd., Jan. 31, 1924).

In the period of complications in cancer, arsenic is of value, especially in the form of injections of sodium cacodylate or the intravenous use of arsphenamin in bi-weekly doses of 0.1 to 0.2 Gm. Infection of cancerous ulcerations should be combated with cleanliness, iodine or Dakin's solution, and the ultra-violet rays. Hemorrhage may be treated by pressure, adrenalin, calcium chloride in 5-Gm. (75-grain) doses, or in particular, intravenous injections of 10 to 30 c.c. ( $\frac{1}{3}$  to 1 ounce) of 30 per cent. sodium citrate solution. In hepatic insufficiency, a milk diet is in order. Renal complications are treated with methenamine, low-protein diet, diuretics, heart stimulants, purgation or venesection. Pain may be

treated by **injection of alcohol** into **nerve trunks**, **intraspinial injections of cocaine**, **heat locally**, etc. **Morphine** should be used with great caution and reserve. M. Renaud (Paris méd., Feb. 16, 1924).

In pain due to deep carcinoma of the face involving the trigeminal branches, **avulsion of the posterior root** of this nerve gives effective relief; also, by rendering the area anesthetic, it permits extensive treatment of the growth without discomfort. For involvement of the cervical plexus and roots **ligation of the posterior roots of the cervical nerves** has been successfully car-

ried out. When an invading tumor enters the distribution of the 9th nerve, causing pain, **section of the petrous ganglion** of this nerve is possible. In this last condition pain is at times referred to the ear and there is a severe burning or scalding sensation confined to the soft palate and pharynx. T. Fay (Amer. Jour. of Roentg., July,

